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<p>The papers in this issue of <u>Present Concepts</u> offer insight into both broad and specialized areas of Nephrology. In several presentations, comprehensive reviews, not elsewhere available, are presented. A mixture of theoretical and practical ideas has been embodied in the majority of articles so that understanding would precede future decision in any of these areas.</p> <p>The first article is another approach to the problem of fluid and electrolyte balance correction of pathologic deviations. Cookbook types of therapy are specifically not included since they have little value to the individual patient. Sufficient emphasis is made on basic concepts so as to enable rational decision. The physician's presentation of his experience in caring for acute renal failure patients off the coast of Vietnam is both rewarding and disillusioning since post-traumatic renal failure is associated with excessive mortality. The excellent report on the pathogenesis of glomerular disease is a timely fact-laden dissertation with immediate value for understanding the immunologic events occurring in patients with glomerulonephritis, lupus nephritis, and Goodpasture's syndrome. An article on malignant hypertension provides objective evidence which solidifies the need for treatment to normotensive levels even if glomerular filtration rate falls, albeit transiently. The discussion of pyelonephritis presents new facets of diagnosis which should be beneficial to every clinician. The last article is a paper on drug abuse and is published as a needed aid in diagnosis and treatment of this extensive contemporary problem. Immediate application is obvious and pitfalls are properly described.</p> <p>Four full-page, black and white, cartoons appropriate to the subject are included.</p>			

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INFECTION, urinary tract						
DRUG ABUSE, acute intoxication						

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## PRESENT CONCEPTS IN INTERNAL MEDICINE

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**VOLUME IV**                      *September 1971*                      **Number 9**

**NEPHROLOGY  
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**FORTHCOMING SYMPOSIA. . .**

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*Present Concepts, Vol IV No 9, September 1971*

## FORWORD

The several papers found in this issue of *Present Concepts* offer insight into both broad and specialized areas of Nephrology. In several presentations, comprehensive reviews, not elsewhere available, are presented. A mixture of theoretical and practical ideas has been embodied in the majority of articles so that understanding would precede future decision in any of these areas. It is hoped that this volume will make a useful addition to the Internist's bookshelf.

The first article, by Rubini and Chojnacki, is yet another approach to the problem of fluid and electrolyte balance correction of pathologic deviations. Cookbook types of therapy are specifically not included since they have little value to the individual patient. Sufficient emphasis is made on basic concepts so as to enable considered, rational decision. Doctor John Conger's presentation of his experience in caring for acute renal failure patients off the coast of Vietnam is both rewarding and disillusioning since post-traumatic renal failure is associated with excessive mortality. As in previous reports, patient chemistries often improved with dialytic treatment while infectious complications precluded survival. Doctor Steinmuller's excellent report on the pathogenesis of glomerular disease is a timely fact-laden dissertation with immediate value for understanding the immunologic events occurring in patients with glomerulonephritis, lupus nephritis, and Goodpasture's syndrome. Doctor Schwartz' article on malignant hypertension provides objective evidence which solidifies the need for treatment to normotensive levels even if glomerular filtration rate falls, albeit transiently. Doctor Michael Conger's discussion of pyelonephritis presents new facets of diagnosis which should be of benefit to every clinician. Finally, Doctor Shiraberger's paper on drug abuse is proudly published as a needed aid in diagnosis and treatment of this extensive contemporary problem. Immediate application is obvious and pitfalls are properly described.

MAJ RICHARD E. CHOJNACKI, MC  
*Guest Editor*

*Present Concepts, Vol IV No 9, September 1971*

FORGET THE HISTORY AND PHYSICAL,  
IS HE MAKING ANY URINE ?



*Present Concepts, Vol IV No 9, September 1971*

## PRINCIPLES OF PARENTERAL THERAPY\*

Milton F. Rubini, M.D.† and Richard E. Chojnacki, M.D.

The physiologic mechanisms of normal water and electrolyte turnover involve intake, absorption, body distribution, and ultimately, excretion. With parenteral therapy, physiologic controls of intake and absorption are bypassed, and homeostatic regulation is largely dependent on renal excretion. Iatrogenic decision must fall between the limits of renal capacity of conservation to minimize depletion, and enhanced excretion to dissipate surfeit. With normal renal function, there is substantial leeway in adequate parenteral therapy, but it behooves the physician to be ever wary of overdependence on renal adjustments to correct therapeutic errors. Errors of omission are only partially compensable by conservatory mechanisms of the kidney, because there is an inexorable loss of water and solutes that eventually must lead to depletion; errors of commission can be rectified only to a degree by appropriate renal excretion. Temporal limits to such compensation are also inherent, and coincident demands for conservation of one substance and excretion of another may be competitive, so that one corrective action is only at the expense of another. There are many examples of apparently discordant renal response. Thus, in order to conserve potassium, an acid urine may be excreted despite alkalosis. Under certain circumstances, the body sacrifices tonicity to maintain volume, e.g. the salt-free urine despite hyponatremia of dehydration, or the sodium diuresis despite hyponatremia of chronic water intoxication. In others, tonicity is protected at the expense of volume, e.g. salt retaining states with impaired water diuresis despite edema.

This discussion of certain practices of parenteral fluid management is more appropriate in principle rather than in specific example. Therapy of a single patient requires cognitive decision based on a variety of individualized data and

\*From Department of Medicine, Wadsworth Veterans Administration Hospital and University of California at Los Angeles. Doctor Chojnacki prepared this article with Dr. Rubini during the year he was associated with Wadsworth before returning to Letterman in 1970.

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circumstances rather than any predefined formula or routine. Such recipes for parenteral therapy by necessity minimize interactions between concurrent homeostatic disruptions, and assume that specific indications predicate similar therapeutic actions consistently. In addition, a baseline of "normal" is inferred, as if all acute and chronic physiologic alterations were a distortion of the steady state of the healthy person. However, chronic disease may define a new baseline of homeostasis, and parenteral treatment of the sick patient often must be directed to re-establish that steady state. The imposition of a preconceived state of normality deduced from the study of well people may be as abnormal for that patient as the acute disorder prompting active therapy. An attempt has been made to focus consideration of this chapter to the more severe and extreme derangements of water and electrolyte metabolism as well as steady-state requirements because it is in these clinical settings that sound and effective parenteral management is most critical.

#### GENERAL PRINCIPLES

Parenteral requirements may be arbitrarily divided into three components: maintenance therapy, deficit therapy, and replacement therapy. Appropriate parenteral therapy requires consideration of each of these three aspects concurrently to promote or maintain fluid and electrolyte homeostasis.

Maintenance therapy is the provision of basal requirements of fluid, electrolytes, and, eventually, calories, trace minerals and vitamins, et cetera. Homeostasis demands sufficient fluid for the excretion of wastes, the stabilization of body temperature by water loss through the skin, and the repletion of respiratory losses. This quantity is often termed the obligatory water requirement, i.e. the maintenance requirement for fluid in its minimum rather than optimal sense.

Basal electrolyte requirements are minimal as efficient renal compensatory mechanisms are evoked with moderate deficits, and the rate of further depletion is minimized. Losses in the feces and in sweat are normally a minor fraction of total excretion. They also are diminished with depletion, but with less efficiency than urinary losses. With abstinence of intake, the bowel and skin losses become major determinants of deficits.

Basal requirements of water, sodium and potassium may be derived from TABLES I and II. The obligatory water loss is the difference between minimum losses and the water of oxidation. Obligatory electrolyte losses are the minimum losses in feces and urine, plus the several mEq/day lost from the skin surface as will be subsequently discussed. Such minimums assume a state of continuing depletion and hence they are theoretic rather than finite.

Homeostatic requirements for water and electrolytes cannot be inferred from maximum concentration of these substances in urine. Thus, the familiar concentration test performed under paraphysiological stress such as water deprivation cannot be continued indefinitely. While man can concentrate his urine to approximately 1400 mOsm/L, the maximum intake concentration of total solute is approximately 600 mOsm/L. Maximum intake is compared to maximum excretory capacity expressing both values as concentrations. Figure 1. Intake concentration is based on maximum infusion concentration that permits a steady state; output concentration is the approximate ceiling concentration of these solutes in urine obtained under a variety of circumstances.

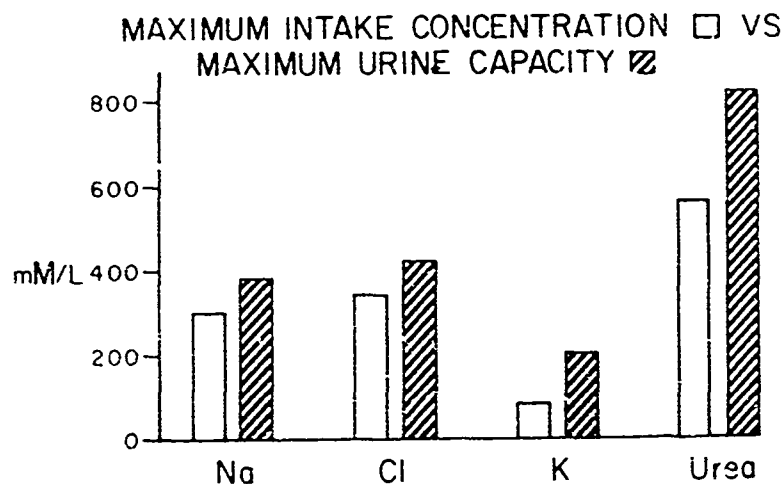


Figure 1.

TABLE I  
DETERMINANTS OF WATER BALANCE

	USUAL RANGE milliliters	EXTREME
Intake		
Foods, liquids*	1000-1500	20,000†
Oxidation of food or tissue	500- 800	2,000
Output		
Urine	400-1200	10,000‡ 15,000§
Lungs	500- 600	2,000
Skin (sweat)	300- 500	15,000
Feces	50- 100	10,000¶
Stomach           Aspirate		6,000
High bowel       or		8,000
Low bowel       Fistula		5,000
Water turnover as percent body water / 24 hours		
Adult	4-20%	
Infant	15-35%	

\* including pre-formed H<sub>2</sub>O

† as water diuresis - diabetes insipidus

‡ as osmotic diuresis - massive glycosuria or sustained mannitol diuresis

§ acclimatized man performing heavy physical effort in dry tropical environment

|| cholera

TABLE II  
CONSERVATION OF SODIUM AND POTASSIUM

	MINIMUM CONCENTRATION OR AMOUNT/DAY	TIME REQUIRED TO ACHIEVE MINIMUM LOSSES	CIRCUMSTANCES
Sodium			
Urine	(1 ml q/l	1-2 days	abstinence + mineralocorticoids
Feces	4-5 ml q/day	>1 week	abstinence + mineralocorticoids
Stomach*	60 ml q/l	immediate	concentration increases with pro- longed aspiration
Bowel†	120 ml q/l	immediate	concentration increases with pro- longed aspiration
Sweat	1 ml q/l	several weeks	acclimatization and profuse sweating
Potassium			
Urine	3-4 ml q/l.‡	2-4 weeks	K deficiency
Feces	2-4 ml q/day	2-4 weeks	K deficiency
Stomach	2-4 ml q/L	days	concentration falls with protracted losses
Bowel	2-4 ml q/L	days	severe potassium deficiency or pro- longed aspiration
Sweat	2-3 ml q/L	several weeks	K deficiency

\* assuming maximal acid secretion

† all bowel aspirates are essentially isotonic but with progressive losses there is increasing exchange of Na for K, and Na composition aspirate approaches that of plasma. Lower values may be obtained if water is used for flushing or if ingested water is lost before it is absorbed

‡ values below plasma concentration may occur with maximal water diuresis but net loss is greater.

Deficit therapy is replacement of losses that have occurred before the onset of therapy; these are finite losses, and can be estimated from direct assays, laboratory findings, history and physical examination. Deficit requirements involve both quantitative and qualitative considerations. Thus, the same quantity of sodium may be administered to correct a deficit of body sodium content in a patient with hypovolemia and a normal or high plasma sodium concentration as is required to replace a deficit in body sodium in a patient with hyponatremia and edema. In the former instance, sodium should be given in sufficient water to expand the extracellular fluid, and hence normal saline might be a logical prescription. In the latter, relative or absolute water excess is evident, so that if salt is deemed necessary, hypertonic saline should be administered as a 3 or 5 percent sodium chloride (NaCl) solution.

Since gastrointestinal losses are most commonly the cause of deficit, knowledge of the volume lost and its probable composition is critical to estimate repletion requirements. Typical losses are depicted in TABLE III; more extensive depletions can be estimated from the maximum volumes in TABLE I as electrolyte losses are generally proportionate. As noted in TABLE III, comparative indices provide a simple estimate of the percent of sodium replacement which should be given as sodium bicarbonate or its equivalent by subtracting 100.

TABLE III

## ACID BASE INDEX OF GASTROINTESTINAL FLUID DEFICITS

Aspirate Derivation	Index: $\frac{(\text{Na})}{(\text{Cl})} \times \frac{100}{140} \times 100$
Stomach	50-90*
Saline	80
Plasma	100     Arbitrary
High intestine†	120-140
Low intestine	150-200

\* Values from 50-120 can usually be considered suited for repletion with normal saline (Index 80)

† Pancreatic secretion is highly alkaline except in the case of fistulae when it is generally admixed with acid stomach fluid

Replacement therapy is the repletion of continuing abnormal losses. These may involve losses through the kidney, gastrointestinal tract, skin or lungs. Again, not only must the volume of fluid lost be replaced, but the composition of the replacement solution should be "tailored" insofar as possible to the composition of the fluid lost. Replacement therapy is always a supplement to maintenance therapy, and may be a complement to deficit therapy. As a generality, losses of fluid derived proximal to the duodenum are acid and tend to make the extracellular fluid alkaline (alkalosis); losses from progressively more distal sites are alkaline tending to leave the extracellular fluid more acid (acidosis). The site of derivation rather than the site of removal characterize the pH and bicarbonate content of gastrointestinal aspirates.

#### *The Concept of Zero Balance*

The steady state of homeostasis is often referred to as "zero external balance" whereby intake and output of a substance are equal. Zero balance also implies normal body content as it is assumed that if an excess or deficit were present, and intake continued, output would adjust to compensate. It is obvious that this concept is an oversimplification, but it is clinically useful and convenient to describe body homeostatic mechanisms and derangements in terms of positive, negative, or zero balances.

Physiologic balance must be defined not only in terms of external balance or whole body content of fluid and various electrolytes, but the internal compartmentalization of these contents, i.e. cellular and extracellular distribution. When either the external or the internal balances are deranged, there is a tendency to return both balances to zero coincidentally, as the content of cells are in equilibrium with the content of extracellular fluids. The fact that a load of isotonic saline is excreted, despite unchanged extracellular concentration, unequivocally points to a volume stimulated regulation of balance.

Diverse contemporary homeostatic mechanisms are always integrated. Distortions of both external and internal zero balance are not only quantitative but also involve the content of one substance relative to another, i.e. concentration of a

solute in extracellular water or the relationship of intracellular potassium to sodium. Appropriate renal compensation to achieve zero balance is often a complex process. Consider the renal adjustment to the prosaic act of infusion of a liter of isotonic salt solution, i.e. 1000 ml of water, 150 mEq of Na<sup>+</sup>, and 150 mEq of Cl<sup>-</sup>. The kidney must not only excrete the load of water and solute in toto, but must be concerned with the temporal relationship of the excretion of one solute as related to another, as well as their concentration in the loading fluid. In the case of isotonic sodium chloride in which the chloride is in substantial excess of its concentration in the extracellular volume, urinary chloride output increases prior to the increase in urine flow; water is then excreted in excess of the extra solute and finally sodium and to a lesser degree, chloride is excreted in excess of extra water.

Despite the wide range of qualitative and quantitative renal adaptation it is easily possible to exceed renal compensation and a chronic overload may develop. Excretory adjustments are often interrelated, the most obvious example being the accumulation of water when the amount of salt given concomitantly exceeds renal excretory capacity.

#### WATER

The first order of concern in parenteral requirements and therapy is water. Normal water balance may be defined as the physiologic state wherein intake is approximately equal to output when neither intake nor output is manipulated. Because intake is usually intermittent and output continuous, an arbitrary period of reference of 24 hours is usually assumed. Water balance is never static, and continuously fluctuates in reflection of activity and metabolic state. Thus, if one assumes that zero balance is reached at a specific time, i.e. at meal times, a normal man subsequently either ingests a water excess stimulating regulatory mechanisms to reduce positive water balance or undergoes water privation stimulating thirst and renal conservation of water.

As a dynamic concept, water balance cannot be arbitrarily defined relative to body weight, intake or excretion without reference to the coincident balance of sodium and chloride.

The temporal as well as quantitative aspects of derangements of water balance are critical to the physiologic and pathologic responses so induced. While the main regulatory mechanism of water balance is renal, overwhelming excess or deficits of water may ultimately cause a renal response which is inappropriate or converse, e.g. antidiuresis of severe water intoxication or the reduced solute output (and isotonic oliguria) that occurs with massive salt excess. Thirst also regulates water balance, albeit at a primeval level. In the activity pattern and conscious behavior of modern man, inhibition is chiefly by habit or custom rather than from thirst.

Water balance is intimately related to thermal balance. In order to maintain thermoneutrality, heat loss over any period must equal the total heat produced. A healthy, active male in a comfortable environmental temperature will lose approximately 1000 calories per day by evaporation of water from the skin and lungs. Additional losses include 2000 calories by radiation and conduction from the skin and 100 calories by increase in temperature of inspired air and excretion. Heat dissipation favors convection and radiation routes in the presence of low ambient temperatures, while evaporation is of prime importance when ambient temperatures are equal to or greater than body temperature. In this situation heat cannot be radiated and heat loss is primarily by evaporation of water from lungs and skin. Each milliliter of water vaporized requires a dissipation of 0.58 calories. Loss of heat from the body is dependent on the amount of water evaporated, not on the amount of sweat produced.

Even in the absence of sensible sweating, water requirements are directly proportionate to the caloric expenditure. An adult metabolizing 30 cal/kg/24 hr utilizes approximately 100 ml H<sub>2</sub>O/100 cal or 2.0 liters. This ration of fluid required per calories expended is relatively constant in most mammalian species, while caloric requirements per kilogram of body weight evolves progressively through infancy and childhood and varies substantially among different species. As metabolic rate is proportionate to surface area, rather than body weight, water turnover can be similarly expressed in all species at about 1100 cc/m<sup>2</sup> of body surface/24 hr. Increased caloric requirements, as in protracted fever or thyrotoxicosis, impose an additional but proportionate water requirement since basal metabolic rate increases 13 percent for each degree rise in body temperature.

The obligatory volume of urine is determined by the amount of solutes that must be excreted and is relatively independent of water ingestion or abstinence, e.g. if daily solute load is 300 mOsm, and maximum urinary osmolality is 1200 mOsm/kg, 400 ml urinary water is required to excrete this load. With greater solute loads, maximum urine osmolal concentration falls, and the obligatory volume of urine increases more nearly geometrically than linearly. Massive glycosuria may impose a solute load of several osmoles per day. Skin losses of water may increase 10-20 fold with physical exertion in a hot dry environment; fecal losses may increase 3-4 fold with diarrhea, and much more with choleraic states. In such abnormal circumstances, water balance tends to lag negatively, and zero balance is approached, but seldom reached by greatly augmented intake under the provocation of thirst alone.

Generally, the urine is more concentrated than plasma, indicating that a mild degree of dehydration is the normal steady state. Even under ordinary circumstances, man drinks episodically in excess, and swings intermittently into positive balance. He then excretes free water to correct an excessive water load. It is the aim of parenteral therapy to maintain a slight positive balance of water so as to allow a modest facultative urinary excretion, i.e. that volume of urine in excess of obligatory excretion. Facultative water is not identical to free water excreted, although free water is always facultative. Urine is therefore generally less concentrated than it could be and still maintain solute excretion. This is probably normal in a physiologic sense as a number of mammalian species from rats to man maintain an intake of water in modest excess of obligatory losses.

The intake of water is in four forms: (1) that water drunk in response to thirst stimuli or habit to meet the cultural patterns, (2) that water which is pre-formed in foods and taken primarily in satiation of hunger, (3) that water which is derived from the oxidation of tissue constituents, and (4) that water which is infused or otherwise introduced into the body by prescription. The character of the diet relates to water available for excretion by the type of food eaten (pre-formed water) and the nutrient composition thereof (water of oxidation). Bread contains 20 percent pre-formed water, meats some 75 percent, and vegetables and fruit from 70-95 percent. The water obtained from oxidation

depends predominantly on the amount of hydrogen of the molecule concerned (protein 0.41 cc/gm, carbohydrate 0.55 cc/gm, fat 1.07 cc/gm). Approximately 12 ml of water are derived from each 100 calories metabolized (protein 10.5, carbohydrate 13.8, fat 11.5 ml/100 cal).

In addition to the quantitative aspects of water balance, there is also a temporal aspect. An increasingly negative balance of water, produced at a modest rate, may lead to well tolerated contraction of body water although a rapid loss of similar magnitude caused by sweating may cause collapse. Chronic water excess may be totally asymptomatic and manifested only by reduction in serum osmolal concentration or it may produce a crescendo of symptoms from mental confusion to eventual coma. A load of water may induce water intoxication if given so rapidly that renal compensatory mechanisms lag substantially in excretion. Acute water intoxication evokes a striking syndrome complex marked by restlessness, acute weakness, diarrhea, salivation, itching and vomiting, tremor, muscle twitches, and convulsions. Forced acute water poisoning has been awarded a reputation as a medieval or oriental torture although it is potentially lethal, the discomfort is short lived and coma rapidly supervenes. The acute syndrome is primarily seen when large water loads are introduced into the gastrointestinal tract and probably reflects rapid loss of sodium and chloride into the intestinal tract, as well as the hemodilution and hypo-osmolality caused by water absorption. Positive water balances produced more slowly by ingestion of similar volumes are seen in psychiatric illness with compulsive water drinking and yet with much less adverse symptoms even though a positive balance of 20 percent of body water may be noted. The central nervous symptomology of water excess is in many ways similar to that of water deprivation, and at extreme, both may be associated with oliguria. Epileptic subjects are particularly prone to seizures with overhydration, and it is reputed that Napoleon "encouraged" ingestion of water as a means of separating potential epileptics from his drafted recruits.

There is also a poorly understood phenomenon of resistance to water intoxication that cannot be completely related to augmented renal excretion. It is demonstrable by giving rats progressive increments of water on successive days and finding an increased tolerance to acute water intoxication that is manifested before diuresis and even after nephrectomy. Glucocorticoids have similar effects, at least in the rat, of

inducing resistance to coma produced by massive water loading. In this species, and possibly in man, adrenalectomy increases susceptibility to acute water intoxication. The situation seems akin in man to the clinical tolerance to hyponatremia which clearly depends on the rate of development as well as the degree.

#### ISOTONICITY AND OSMOLALITY

Successful parenteral therapy requires not only restoration and maintenance of volume but also a normal solute concentration in that volume. Solutions which are at the concentration of plasma and extracellular fluids are "iso-osmolal" or "isotonic" although the latter term is often used incorrectly.

Isotonicity of a solution is defined as that concentration at which suspended red cells are unchanged in volume. Tonicity is independent of osmolality, e.g. the addition of urea or alcohol to an infusion does not alter tonicity because these substances freely permeate red cells and yet such addition obviously alters osmolality. Tonicity is defined relative to a membrane of reference, while osmolality is a colligative property of a solution whether or not a membrane is present. Isotonic solutions are not necessarily of the same osmolal concentration as the fluid within the cell and categorization of isotonicity depends to a degree on the species of mammalian cells utilized. Thus, rabbit erythrocytes define isotonicity at 1.1 percent sodium chloride, while 0.9 percent sodium chloride is isotonic for human red cells. The clinical use of isotonic saline implies a matching with the osmolal concentration of the extracellular fluid. This is only partially true, however, as the effective osmolal concentration of the fluid bathing cells is some 5-10 percent lower than that of isotonic saline, and may vary  $\pm 5$  percent from patient to patient.

Plasma is the conduit between the protoplasm and fluid leaving or entering the body. As plasma is isotonic by definition, only fluid containing a suitable concentration of solute can traverse the plasma. It is this coincident solute movement that controls the flow of water across biologic membranes and is influenced by simple diffusion, hydrostatic pressure, cellular metabolic activity and trans-membrane ionic fluxes.

The complexity of (transmembrane) water and salt movements is exemplified by the changes which occur in the volume and composition of fluids introduced in the peritoneal cavity. Isotonic glucose solution increases in volume prior to absorption because of the transperitoneal movement of sodium and chloride which temporarily raise osmolality above that of plasma. Isotonic saline by contrast is readily absorbed, and only by the addition of 3.5 to 4 percent glucose may the absorptive forces be balanced. The dependence of water movement on the character of solute dissolved may be further illustrated in several simple physical-chemical experiments: (1) isotonic saline will lose fluid across a cellophane membrane to isotonic glucose because cellophane as compared to the red cell membrane is more permeable to salt than glucose, and (2) when isotonic solutions of magnesium sulfate and sodium chloride are similarly separated, the sulfate side expands at the expense of the chloride side, reflecting the different rates of solute diffusion, i.e. chloride diffuses faster than sulfate.

#### PROCEDURE OF PARENTERAL THERAPY

The first requirement for parenteral management is a safe and ready access to the circulation. Indwelling venous catheter techniques have greatly simplified procedure, but care must be constantly applied to avoid introduction of infection by use of bactericidal ointment at the site of skin puncture. Continuous infusion minimizes the risk of clotting while peripheral venous catheters should not be used for more than a week (preferably 3-4 days) without changing the site of infusion. Solutions of glucose above 14 percent are poorly tolerated in peripheral veins, but introduction of a catheter into large deep veins such as the jugular, the iliac, or even the vena cava, permits the rapid dilution of more hypertonic solutions which otherwise tend to injure the venous intima. The addition of glucocorticoids to commercial hypertonic infusion solutions, presumably to minimize inflammatory reaction, is probably unnecessary but seems harmless. Heparin in small amounts also may be added to hypertonic infusions.

As a general principle, single component solutions are preferable to polyionic solutions if several solutes must be given simultaneously. The addition of potassium chloride or sodium bicarbonate in specific and carefully considered

amounts to isotonic saline is preferable to "standard" mixtures prepackaged for marketing convenience rather than physiologic merit. All additives should be labeled on the infusion bottle and orders should define rate of administration, the character of parenteral fluids, and volume prescribed. Bottles should be consecutively numbered to minimize confusion and to readily permit bedside recognition of the speed of administration. The nursing staff should be alerted to recognized changes in urine flow, thirst, anxiety, headache, and others, as probable indications to slow but not completely stop the infusion and to notify the responsible physician. The use of indwelling central venous catheters to determine pressure at frequent intervals is helpful when the volume required is uncertain or renal compensation is limited, especially in elderly or debilitated subjects. Fortunately there is a wide flexibility of physiologic adaptation to overzealous application of parenteral therapy so that a trial and observation routine is generally feasible.

Laboratory studies needed for rational parenteral management include the hematocrit, and the sodium, potassium and bicarbonate content of plasma. Plasma or blood pH determined either electrometrically or indirectly from  $pCO_2$  and bicarbonate is especially helpful. Osmolality of plasma may be invaluable, especially for recognition of circulating osmotic material other than sodium, such as mannitol or urea. The chief contribution of plasma chloride determination is in relationship to sodium concentration, and serves to delineate states of anion excesses occurring in uremia or lactic acidosis. Urine studies of prime utility include a measure of concentration (osmolality is preferred to specific gravity) and pH. Unless there is obvious excessive loss of body fluid, plasma determinations are more essential than random determinations of urinary electrolytes.

In chronic disorders of body fluid and electrolyte balance, once intake is known, the determination of sodium, potassium and chloride content of spot samples of urine is increasingly valuable, but 24 hour collections are superior. The cognizance of external electrolyte losses from all liquid excretions and aspirations from the body is essential, and continuous complete daily collections should be obtained. The physician must consider the delay in obtaining the collection and the time required for laboratory studies in the interpretation of the patient's status of the moment.

Parenteral therapy should be carefully re-evaluated at least daily, an approach facilitated by accurate tabulation and charting of pertinent data. Too often, decision is made predominantly from laboratory data. The wary clinician, however, should never regard the laboratory as more than an adjunct to information gained directly by clinical observation of the patient because even with reliable data and reasonable deduction, the patient will sometimes show clinical deterioration before or despite biochemical improvement.

#### Parenteral Therapy of Hypo-Osmolal States

The symptoms of hypo-osmolality are non-specific and include weakness, lethargy and coma. Intracellular hydration is increased except possibly in certain chronic disease states associated with proportionate intracellular potassium losses "the sick cell syndrome". Clinical dependence on such signs as skin turgor or fingerprint clarity may be inadequate, especially in the elderly. As red blood cells swell, hematocrit may be elevated. Cerebral spinal pressure may be moderately increased but papilledema is unusual. The electroencephalogram may show non specific slowing. Thirst occurs despite hypo-osmolality in response to acute changes in volume, toxicity, or possibly potassium deficiency. Urinary sodium is usually not helpful diagnostically as it may be reduced (secondary to reduction of filtered load?) or increased.

In most instances, water deprivation alone is optimum therapy. This is more easily prescribed than expedited as the hospital environment is permeated with the idea that forcing fluids is an attribute next to cleanliness. Cracked ice and liquid nutrients are proffered indiscriminantly by well meaning aides, visitors, and other patients who seem to equate thirst with neglect. More rapid correction of plasma osmolality requires the administration of hypertonic salt solutions. This option depends on definite acute clinical indications because pulmonary edema, congestive heart failure and hypertension may ensue, especially if whole body sodium is already increased. With treatment, the rise in serum sodium will be predicated on the redistribution of water, and not simply the dilution of sodium in a static extracellular fluid volume. Therefore, whole body water must be used to calculate the amount required to achieve the desired change in concentration. In most instances, such calculation indicates a need for very large quantities of hypertonic saline

to raise concentration to normal, much to the consternation of the physician. A trial of 25-50 percent correction is usually sufficient to demonstrate whether clinical improvement will occur. Administration should be slow, preferably over a 12 hour period followed by a 12 hour period of observation. As a rough guide, 6 ml of water becomes isotonic for every millimole of sodium chloride given in excess of normal saline. Sodium excretion in the urine may remain unchanged until the body deficit is replaced or may increase under the stimulus of expanded volume or the persistence of an altered "osmostat".

The removal of water in excess of salt may be accomplished by inducing an osmotic diuresis, usually with mannitol. The concentration of urinary sodium during vigorous diuresis with this agent is approximately 30-40 mEq/L, so that three-fourths of urine volume is in excess of the osmolar ratio of plasma. Urine flow, however, is proportionate to the filtered load of mannitol so that a substantial plasma mannitol concentration is necessary. Increasing plasma osmolality in this manner may reduce cerebral edema by establishing an osmotic gradient. Rebound phenomena are minimized as the excess water drawn from cells is carried into the urine. Because plasma volume expands initially with large mannitol loads, the procedure is not entirely without risk of pulmonary edema. Barry, however, recommends the use of mannitol, at least in a trial dose of 20 grams, in most patients even in the presence of mild to moderate heart failure. /1/ Urea may be similarly employed but rapid infusion of concentrated solutions of urea may provoke nausea, vomiting and somnolence. Urea slowly enters cells and, as urea is excreted into the urine and extracellular fluid concentration falls its subsequent diffusion back into the plasma may lag behind that of water and central nervous system symptoms may be aggravated.

Concentrated glucose infusion may also be effective, but the high blood sugar levels needed to induce a brisk osmotic diuresis are not well tolerated and require massive loads. Finally, the induction of sweating is more of a theoretic possibility than a practical measure for application in sick patients.

### Parenteral Therapy of Hyperosmolar States

Clinical recognition of hyperosmolar states is based on intuition and knowledge of precipitating factors. Symptoms that are suspect include somnolence, lethargy, or coma (a rather similar picture to the symptoms of hyponatremic states). Restlessness, anxiety and even manic activity may be premonitory manifestations, headache or visual difficulties may be prominent. Precipitating factors include diabetes and water deprivation.

The skinfolds are lax and normal skin elasticity is lost, sweating stops. Subcutaneous tissue is plastic and thin, the mucous membranes are dry and saliva is scanty. Vaginal mucosa is also dry, a finding that may be useful diagnostically in female patients breathing through their mouths. The patient may have a staring appearance and the voice may be hoarse. There is a general apathy and delayed response to interrogation. Thirst may be a complaint upon direct questioning, but because the patient is often severely ill and stuporous, its presence is often not spontaneously ascertained. Recumbent hypotension may be prominent, or postural hypotension and faintness may be the chief reflection of hypovolemia. Cold extremities, thready pulse, collapsed veins may also be present, ocular tension may be diminished on palpation.

Confirmation is obtained by the demonstration of elevated plasma sodium or osmolality. Azotemia raises plasma osmolality but effective osmolal concentration is normal. Increased circulating lipid or protein may artefactually raise serum sodium due to displacement of plasma water. A true hyperosmolar state may be due to substantial hyperglycemia, e.g. greater than 500 mg/100 cc (180 mg/100 cc = 10 mOs/L), while lower blood levels have less importance except for the aggravation of water and salt by losses by osmotic diuresis. With hyperglycemia, plasma sodium is not a reliable indicator of hyperosmolality since it accounts for less than its usual half of total plasma solute. Excessive sweating, hypertonic or dry salt administration are occasional causes of hyperosmolality, but most cases are due to water deprivation or to an excessive obligatory loss of water secondary to solute overload.

The classic example of hyperosmolar hypovolemia is an older patient with nephrosclerosis who is unable to concentrate his urine normally. Admitted to the hospital and unable to eat by himself, he is started on a tube feeding mixture. Too often, the emphasis is on total calories, protein, vitamins and electrolytes so that water needs are neglected. The inability to conserve water is further compounded by the fixed loss of water accompanying increased urea nitrogen excretion. With hypovolemia, salt retaining stimuli are added. On the fourth or fifth hospital day, the patient has lapsed into coma and serum sodium is found to be 165 mEq/L. A myocardial infarct or cerebral vascular accident that was suspected as the cause of deterioration may have actually been induced by dehydration, thus further complicating recognition of the original cause of difficulty.

Hyperosmolality is often (but not necessarily) coincident with hypovolemia and the symptomatology of increased concentration merge with that of decreased volume. Hypovolemia due to loss of whole blood volume is discussed subsequently in the subsection on acute volume deficits. The commonest clinical cause of hypovolemia and ultimately hyperosmolality is dehydration, a clinical term applied in a broader sense than simple desiccation.

The recognition of dehydration is facilitated by characterization of urinary output. With dehydration, urine is characteristically reduced in volume; it is highly concentrated but low in sodium content as the body attempts to conserve volume at the expense of tonicity. These findings do not necessarily prove dehydration, as patients with acute glomerulonephritis may produce a small volume of highly concentrated urine with little sodium. Similarly, acute reduction in renal bloodflow may serve to produce oliguria with sodium retention and increased osmolar concentration. Conversely, the finding of a copious urine volume with increased sodium concentration does not rule out dehydration as renal function may be inadequate or an osmotic diuresis may be present.

The relationship of solute load to water requirement depends on concentrating ability, the rate of solute excretion (that is, the degree of osmotic diuresis) and to a lesser degree, the predominant solute excreted. Prefeeding protein increases concentrating ability, protracted overhydration diminishes it. With reasonably normal filtration rates and usual solute intake, the specific gravity at urine flow greater than 1.5 cc/min

should be less than 1.010. The finding of consistently isotonic or slightly hypertonic urine with outputs of over 2000 cc/24 hr should suggest that an osmotic diuresis is present.

In general, the mainstay of parenteral treatment of hyperosmolar states with hypovolemia is 5 percent glucose in water, although 0.45 percent saline may be used to replete volume when water is needed in excess of salt. Isotonic intravenous glucose solutions may be infused at a rate of 12 cc/min without producing glycosuria (0.5 gm glucose/kg/hr). This is approximately one-half the equivalent rate tolerated by dogs. The limiting restriction to the rate of infusion of 5 percent glucose is the blood glucose concentration and thus depends on antecedent diet and nutritional status as well as the factors which influence the action of insulin.

For practical purposes, infusions of 5 percent glucose behave as if only water were infused. There is an appreciable lag to diuresis following glucose infusion that is not proportional to the rate of infusion, and hence is not explicable by rate of fall of plasma osmolality or the rate of expansion of body water. This phenomenon most probably represents the lag time for the disappearance of all circulating antidiuretic hormone. Peak diuresis, on the other hand, is directly related to load and loading rate. Diuresis persists after cessation of infusion for a one to two-hour period, independent of the amount of positive water balance accrued at the end of infusion, although the amount of urine produced over this period is clearly load-related.

In normal individuals, a diuresis of over 35 cc/min may be achieved for brief periods, but it is difficult to sustain water diuresis above 20 cc/min for protracted periods even with constant water intake. If continuous water intake substantially exceeds the rate of output, urine flow may abruptly fall as symptoms of water toxicity appear. Because there is an apparent floor to solute concentration in urine of about 80 mOsm/L, continuously high urine flows are necessarily solute depleting (especially of sodium and chloride). Hyponatremic and hypochloremic states as well as most chronic debilitating diseases impair the ability to excrete a water load and diuresis may be absent, reduced in quantity, or delayed. Pain, fear and many drugs stimulate antidiuretic hormone (ADH) release and may inhibit the production of free water and excretion of a positive

water load. Thus, glucose infusions are an unreliable therapeutic means of inducing a sustained diuresis, e.g. after drug ingestion, when a high rate of urine flow is desired; an osmotic diuresis with a non-absorbable solute such as mannitol is preferable.

#### Parenteral Therapy of Acidotic States and the Therapeutic Induction of Alkalosis

Severely acidotic clinical states are frequently complicated by coincident azotemia, hypercapnia and hypoxia so that the etiology of specific symptoms is difficult to determine with certainty. The most common cause of severe acute acidosis is the retentive accumulation of organic acids, especially lactic acid or keto-acids due to overproduction or anoxia. Less chronic and usually less severe metabolic acidosis is most commonly caused by protracted loss of alkaline intestinal secretions. Arterial blood pH values below 7.25 are associated with mental disturbances and possibly coma; jactitations, papilledema and arrhythmias may occur. Cardiac output is increased and peripheral blood flow and heat loss is accentuated. Severe acidosis is particularly deleterious in the presence of a borderline cardiac compensation as the greatly increased cardiac demand and the diversion of blood from vital organs may initiate a vicious cycle of acidosis failure anoxia more acidosis, and so on. Death is imminent with a blood pH that is slightly below 7.00.

The aim of therapy is to decrease the causative factors of acidosis, e.g. anoxia, carbon dioxide retention or insulin lack. In addition, sodium bicarbonate or lactate solutions are generally used. Rapid shifts from severe acidosis to overt alkalosis should be avoided because of the risk of inducing arrhythmias. Hypocalcemia with convulsions may also occur with over-correction and rapid production of metabolic alkalosis, especially in children.

The "bicarbonate deficit" is unreliable in assessing the degree of acidosis since other buffers, notably hemoglobin, tissue proteins and possibly the skeleton are involved in compensation of what can be considered a proton load. To estimate the bicarbonate needed, a general rule of thumb is to subtract the observed bicarbonate from an ideal normal of

approximately 27 mM/L and to multiply this difference by 40 percent of body weight, i.e. a value somewhere between extracellular volume and whole body water. Usually, only half of the deficit is given in the first 24 hours. In situations of extreme acidosis, e.g. methyl alcohol poisoning, it may be desirable to give extremely large amounts of bicarbonate rapidly until urine pH becomes alkaline. Calculation of bicarbonate distribution under these circumstances may reveal a substantial discrepancy between the amount administered and that amount retained in the chloride space or excreted in the urine which confirms the existence of unmeasured cellular buffers.

Intravenous solutions employed to increase plasma pH contain bicarbonate, lactate or acetate. In theory, all are similar because acetate and lactate are rapidly metabolized to bicarbonate. Bicarbonate, or its equivalent, may be given as commercially prepared balanced isotonic solutions, usually containing about 30-45 mOs/L of base excess as one-sixth molar or one molar lactate, or the desired amount of bicarbonate may be added to other fluid requirements. More concentrated solutions of bicarbonate, e.g. five percent, are occasionally employed but lactate containing solutions have generally been accorded the greatest popularity, perhaps due more to familiarity than on a scientific basis. Even though it is produced by fermentation, a process more expensive than chemical, lactate is used preferentially to bicarbonate in the manufacture of balanced solutions that are stored, because bicarbonate solutions tend to decompose with the formation of insoluble carbonates. Available solutions of lactate contain the racemic form of the substance although the metabolism of d-lactate is substantially slower than that of l-lactate. /2/ Lactate and pyruvate concentrations in the plasma may rise temporarily in normal individuals receiving lactate ion. Acetate solutions are more stable and potentially cheaper to produce chemically but have had limited use except for peritoneal dialysis. Plasma lactate and pyruvate do not increase with acetate, and plasma clearance of acetate is rapid. In certain circumstances such as in diabetic acidosis or in uremic patients undergoing chronic dialysis, there appears to be a slowing of the metabolism of acetate ion; hence, limiting its utility.

A special case of acute acidosis is primary lactic acidosis in which the defect seems to be the irreversible conversion of pyruvate to lactate which accumulates in extracellular volume producing a severe, progressive, and often

lethal retention acidosis. Alkali therapy with bicarbonate has been notoriously unsuccessful in promoting salvage suggesting that reduced plasma pH is the misdirected focus of therapy.

#### Parenteral Therapy of Alkalosis

Clinical states of alkalosis are less common than acidotic states and the infusion of acid to correct severe alkalosis is seldom required as an emergency measure. Although respiratory alkalosis is frequent, especially in patients with anxiety or central nervous system injury or disease, the symptoms are relatively minor and may be ameliorated by rebreathing or CO<sub>2</sub> administration. The respiratory alkalosis of salicylate intoxication or liver disease is also due to central nervous stimulation, but these states are complicated by coincident or potential metabolic acidosis and may fare poorly with CO<sub>2</sub> therapy. Metabolic alkalosis is most commonly seen after protracted vomiting, nasogastric suction and diuretic abuse. It may also follow successful therapy of acute pulmonary insufficiency with respiratory acidosis, i.e. patients who have suffered prolonged renal losses of chloride whose alkalosis will persist until the chloride deficit is repleted. In most instances, repletion of chloride ion as sodium chloride is adequate therapy because renal excretion of sodium bicarbonate continues until chloride deficit is abrogated. Coincident potassium deficiency may intensify the metabolic alkalosis (vide infra). When chloride must be given without sodium or potassium, ammonium chloride may be used, except in patients with liver disease who are prone to hepatic coma. Hydrochloric acid may be administered as a one percent solution, or the hydrochloride of arginine or lysine may be given.

#### Parenteral Potassium Therapy

Potassium deficiency is most often due to exaggerated renal loss, e.g. with chronic thiazide administration or secondary hyperaldosteronism. Substantial loss by the way of the intestinal tract is less frequent, e.g. laxative ingestion for many months. Because potassium is effectively conserved by the normal kidney, albeit somewhat less efficiently

than is sodium, clinical deficiency caused by extrarenal loss requires weeks to develop. Equilibrium is achieved with potassium intakes as low as 10-15 mEq/day. Most natural foods contain potassium, hence it is virtually impossible to become deficient because of an inadequate intake of potassium while consuming an ordinary diet of adequate calories and protein.

Hypokalemia is often, but not invariably, found in potassium deficiency states. Sodium balance intimately affects serum potassium and with severe salt depletion, serum potassium may be increased while body potassium is reduced. Although an oversimplified tautology, the physician should recall when potassium leaves the cell, sodium and hydrogen replaces it, and when potassium losses are repaired and potassium enters cells, this ion flux is reversed providing for  $3K = 2Na + 1H^+$ . The association of acidosis and release of cellular potassium into the blood, and of hypokalemia with alkalosis is then understood. Similarly, the renal tubular exchange of potassium or hydrogen ion for sodium characterizes urine pH — when the renal tubular cell is actively conserving potassium, urine is acid; when the renal tubular cell is wasting potassium, it excretes less acid and urine is alkaline. Thus the paradoxical aciduria of metabolic alkalosis associated with potassium deficiency occurs only with extrarenal causes of the potassium deficit. Since diminished ability to concentrate the urine occurs early with potassium deficiency, the finding of an elevated urine osmolality in a patient suspected of potassium depletion should suggest an alternative diagnosis. Urine potassium concentration below 10 mEq/L supports an impression of potassium deficit, and monitoring of urine concentration after parenteral therapy is instituted may be useful. Potassium deficient patients will not excrete infused potassium beyond minimal levels provided sodium reabsorption is not excessive.

The uptake of glucose and production of glycogen by the liver may further reduce serum potassium and glucose infusions may precipitate hypokalemic paralysis in subjects already potassium depleted. For this reason, glucose infusions should be withheld until potassium deficit is substantially repleted and parenteral potassium should be added to saline rather than glucose if severe hypokalemia is evident.

When potassium depletion, with or without hypokalemia, is associated with arrhythmias, muscle paralysis or ileus,

partial rapid repletion of the potassium deficit is desirable. As the amount of potassium which has actually been lost is clinically difficult to estimate short of whole body counting or by isotope dilution, therapy for the patient with normal renal function is primarily directed to give a modest excess of potassium and to depend on renal excretion to adjust for overtreatment. In the presence of oliguria or renal failure, parenteral or even oral replacement therapy must be approached with caution. The potential irreversibility of the renal lesion of potassium deficiency suggests that even modest depletion is undesirable. When clinical circumstance indicates the likelihood of continued potassium loss, especially with symptoms possibly caused by potassium deficiency, the preventive treatment of potassium depletion is justified. If potassium cannot be given orally, parenteral administration is advisable.

The practical approach to parenteral therapy requires a ready willingness to include potassium in parenteral regimens with special attention to correction of coincident deficiencies of sodium and chloride. Once urine flow is assured, and in the absence of accelerated tissue catabolism, potassium can be given in solutions of 20-40 mEq/L at a rate not exceeding 20 mEq/hour.

Kunin et al /3/ and Clementsen /4/ indicate that potassium may be infused at 40-60 mEq/hr provided that glucose is given simultaneously. The presence of severe potassium depletion may limit the rate at which potassium salts may be infused safely. Animals deficient in potassium are readily made hyperkalemic at rates of intake of potassium tolerated with impunity by animals previously fed a potassium excess. TABLE IV. Because hyperkalemia may rapidly develop, electrocardiographic monitoring is advisable with parenteral potassium infusions.

The most common clinical cause of hypokalemia is upper intestinal aspiration. The splinting of the upper gastrointestinal tract by continuous gastric suction is a common procedure of surgical management. That hypochloremic alkalosis and hypokalemia may occur is broadly accepted on most surgical services. The mechanism of such alkalosis, often incorrectly ascribed to the removal of potassium in the gastric aspirate, is a result of the progressive depletion of chloride, as chloride concentration in gastric aspirate is generally in excess of sodium. Because of mild dehydration, hypovolemia and surgical stress, there is a coincident stimulus for sodium

TABLE IV  
DIETARY EFFECT ON POTASSIUM TOLERANCE  
Mortality Figures on Four Groups of Eight Rats\*

K Intake	ORAL STRESS				Intake	PARENTERAL STRESS (100 gm/4hr)		
	1%	2%	5%	10%		0.1 mEq	0.5 mEq	0.1 mEq
Low	0	2	8	8	Low	2	8	...
Normal	0	0	3	6	Normal	1	2	8
High	0	0	1	5	High	1	1	4

\*Rats pre-fed potassium are resistant to potassium stress; rats depleted of potassium are sensitized. Oral stress was induced by the addition to drinking water of increasingly concentrated solutions of KCl for four days. With 2-10 percent solutions, gavage feeding was employed because some rats refused to drink; the volume administered was the average imbibed by the one-percent group.

Parenteral stress was given intraperitoneally in 2 cc volume; sodium chloride was added to the more dilute solutions of potassium to make all solutions equimolar. Nephrectomy increased overall mortality but failed to alter the relative protection of antecedent prefeeding or the sensitivity of antecedent depletion, indicating that the effect is most likely operative at a cellular level. Mechanism of death is unknown but probably due to acute cardiac arrhythmia.

retention. Hypokalemia also reflects the renal adjustment as more potassium is excreted in exchange for sodium in the presence of alkalosis. The degree of hypokalemia is usually moderate and its importance is more to stimulate recognition by the physician of the abnormal physiologic state than to constitute a serious stress to postoperative recovery. If fluid and caloric requirements are met, potassium need not be added for several days.

Potassium concentration in gastric fluid is generally below 20 mEq/L and falls with continuous gastric aspiration. Removal of several liters by gastric suction withdraws from the body less than 100 mEq of potassium, and deficits of this magnitude are tolerated with impunity by the individual not previously depleted. However, the superimposition of glucocorticoid stress under these circumstances may provoke a drop in serum potassium and the development of mild metabolic

alkalosis with minimal change in overall body balance. Similarly, the elevated serum potassium in nephrectomized adrenalectomized dogs allowed to develop an Addisonian crisis is substantially corrected by glucocorticoid administration indicating that the gradient of potassium across the cell membrane is critical to its plasma concentration, independent of whole body content of potassium. With protracted gastric aspiration, parenteral administration of potassium is advisable, especially in patients who have been chronically ill and are likely depleted of potassium before surgery. The problem may become further compounded by the need to administer glucose feedings which promote glycogen production, as serum potassium may decrease further and cardiac arrhythmias may result, especially if the patient is digitalized.

The repletion of potassium losses under these circumstances is dependent not only on the administration of adequate amounts of potassium, but also on the concomitant administration of chloride ion. The use of such potassium supplements as gluconate, citrate or phosphate may fail to correct alkalosis and hypokalemia unless adequate amounts of sodium chloride are also given. As the primary mechanism of alkalosis is chloride deficiency, the use of ammonium chloride or lysine monohydrochloride might be considered and, in most instances, the serum potassium will rise.

The amount of potassium that can be conveniently and safely given parenterally is limited and full repletion of body stores must usually await reinstitution of oral feedings. Ideally, the potassium requirement should always be given by mouth and preferably with normal foods. The institution of a reasonably normal diet will offer at least 60-80 mEq/day. When larger amounts are required, potassium supplements are useful, but enteric coated tablets containing potassium chloride should be avoided, as small bowel ulceration and stenosis have been reported.

The ratio of nitrogen to potassium in protoplasm is consistent from calculations based on losses during starvation, retention during repletion of protein deficiency and from direct carcass and muscle analysis. However, nitrogen can be retained (protoplasm formed?) in absence of potassium. Figure 2.

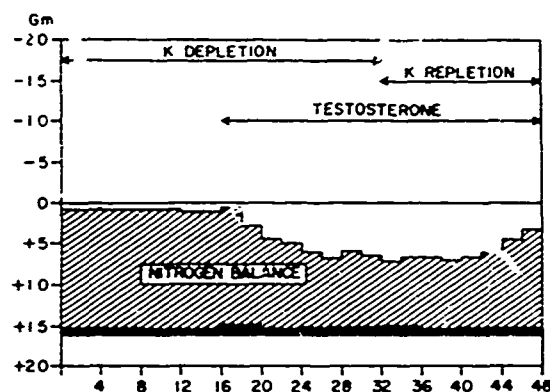


Fig 2 Graphic illustration of testosterone-induced positive nitrogen balance occurring in the presence of potassium depletion.

#### ACUTE VOLUME DEFICITS

The fundamental defect in shock is a reduced perfusion of tissues to a degree insufficient to sustain metabolic function. This may be due to a decline in blood pressure or increase in the peripheral resistance to blood flow as well as to inadequacy in blood volume. The stupor, coldness and pallor of the skin, weakness of the peripheral pulse, and oliguria represent the effects of decreased blood flow to specific organs. In addition to the initial ischemic derangements of primary function, a series of secondary deleterious metabolic effects involving the liver, brain, kidneys and endocrine glands exaggerate and perpetuate the shock state. Accompanying these secondary changes is acidosis, reflecting the altered oxidative metabolism of tissue. From the point of view of parenteral therapy, the critical repletion is that of volume, as the fundamental treatment is improvement of oxygenation of tissues, rather than the temporary correction of pH.

The central blood volume is about 50 percent of whole body blood volume and it is equally divided between the thoracic contents and the splanchnic bed. Approximately 75 percent of the blood is normally contained in the venous system and an additional 12 percent is in the capillary beds. Because veins and capillaries constitute a low pressure system, small changes in pressure may cause striking changes in volume. The converse holds true in the arterial bed where volume elasticity is minor and large changes in pressure may occur independently of arterial volume.

In defense of the plasma volume, extravascular albumin is released from the liver and lymphatics in an attempt to maintain oncotic pressure and thus draw fluid from the extracellular space into the plasma. As the extracellular space is some five times the plasma volume, it may be considered an unlimited volume reservoir provided sufficient protein is available to maintain the necessary oncotic gradient. The plasma protein reserve is modest and probably no more than 25 percent of total body albumin exists extravascularly. The response to acute hypovolemia is therefore limited, and after the plasma protein reserve is mobilized, further correction of hypovolemia depends upon transfusion of albumin or plasma or the introduction of an oncotic equivalent.

A number of plasma expanders have been utilized. These include materials prepared from natural biologic products and artificially synthesized macromolecules. In general, none have proven ideal, and such complications as retention in the reticuloendothelial system, allergic reactions, antigenicity, disturbed clotting, capillary fragility, thrombosis, aggregation and clumping of erythrocytes, and impaired flow through small vessels resulting from increased viscosity have been noted. Artificial expanders such as polyvinyl-pyrrolidone, gelatin, and hydroxyethyl starch have been gradually supplanted by a dextran. Biologic products such as lyophilized plasma and modified human globin have proven less satisfactory than concentrated human albumin.

In burn cases, decreased plasma volume occurs secondary to trapping of plasma outside the normal vascular volume, as well as those losses due to weeping and evaporation. A similar transcapillary exudation occurs with certain bacteremias. With intestinal obstruction, large quantities of plasma and its ultrafiltrate may be rapidly compartmentalized as an unphysiologic "third space" in the bowel lumen. With

barbituate poisoning or endotoxemic infections, massive splanchnic dilatation may trap a substantial portion of the blood volume. In these instances, the parenteral therapy required is substantial and often of massive proportion. Even in these complicated examples of hypovolemia, recognition of the exact cause of shock is often less immediately vital than its alleviation, but ultimately is critical to successful management.

As plasma volume reflects the extracellular volume of which it is an intimate part, decrease in extracellular volume for any cause increases sensitivity to shock; and saline preloading is protective. Figure 3.

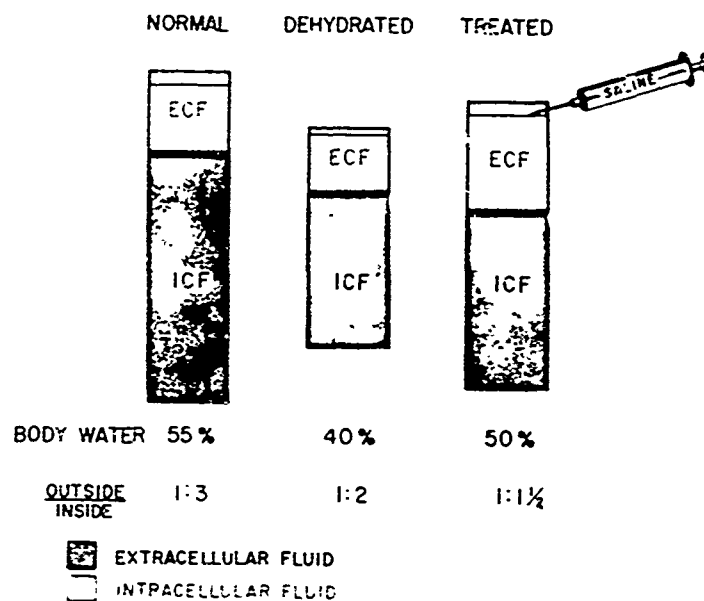


Fig. 3 Relative distribution and compartmentalization of body water in normalcy and in dehydration with and without partial saline replacement.

#### PARENTERAL THERAPY IN RELATIONSHIP TO SURGERY

The management of a patient through surgery is a test of the physician's understanding of fluid and electrolyte problems. Coincident with the direct trauma to tissue may be problems of

anesthesia, immobilization, starvation, protein depletion, dehydration, sweating, renal and cardiac insufficiency. Relative hormonal deficiencies or imbalances involving the pituitary, thyroid, and adrenal glands may develop. Inadequate replacement of acute deficits because of vomiting, diarrhea, upper or lower intestinal aspiration, and others, may complicate the issue.

The immobilized postoperative patient depends upon medical action to maintain body homeostasis. Superimposed is a hazily demarcated syndrome generally termed "the injury reaction". Despite extensive study two decades ago, surprisingly little is known about the mechanism of this catabolic stress. It is composed of a series of physiologic responses that attend surgery and influence fluid and electrolyte management. These responses include an increased urinary excretion of nitrogen, the loss of body weight consistent with the mobilization of fat stores, an increase in body temperature, pulse rate, and oxygen consumption despite a reduction of respiratory quotient, and diminution in urine volume with increased urine concentration. Sodium retention, potassium loss into the urine, hyperglycemia, and increased urea production due to enhanced catabolism of protein characterize these states. Cellular loss of potassium with hyperkalemia and fat mobilization with hypertriglyceridemia may also occur. With diminution of urine output, there is an inability to excrete salt-containing parenteral fluids despite an increased solute load of urea due to prerenal azotemia.

An increased secretion of adrenal corticosteroids could explain many of these findings, but the injury reaction may occur in the adrenalectomized patient receiving constant doses of gluco- and mineralocorticoids and is minimized in the very sick and in the very old. This surgical response is maximal in the robust young, healthy patient undergoing elective surgery. The fact that these physiologic changes are the normal and usual accompaniment of uneventful surgery should be recognized by the physician. Attempts at their modification by large doses of androgens, high protein feedings, and other measures, have been largely temporary in effect. A recent trend has been preoperative anticipatory treatment with loading of water, potassium and protein for repletion of unrecognized deficits. /5/

The duration, as well as the magnitude of the response to surgery depends to a large degree upon the overall health of the patient and the extent and type of surgical procedure

performed. Especially prominent responses occur with invasion of the pleural or peritoneal cavities or with trauma to the skeleton. When surgical complications are superimposed, the pattern of metabolic response to surgery is further altered, and recovery is deferred as starvation and immobilization are prolonged.

Postoperative parenteral therapy depends on the degree of derangement and the time anticipated before oral feedings can be resumed. If recovery is rapid, and postoperative course uneventful, the potentiality of electrolyte depletion may be neglected and a water intake of approximately 1000 cc in excess of urine volume given daily. Preferably, this should be as a 10 or 15 percent glucose solution to minimize protein catabolism. If oral intake must be postponed until the fourth day or longer, modest amounts of sodium may be added to match urinary excretion, remembering that salt retention is the usual acute response to surgery and a natruresis may be prominent during the later recovery phase.

As potassium deficits over 100 mEq may approach pathologic significance, potassium balance should also be considered. Homeostatic requirements of potassium during prolonged parenteral therapy are readily met by the inclusion of potassium parenteral regimen in concentrations of 5-10 mEq/L plus additional potassium to make up known external losses. The amount required must be assessed individually with a concerted effort to give potassium slowly and to implement oral intake as soon as possible.

There may be some advantage of giving phosphate in chronic parenteral therapy because phosphate is the main intracellular anion, and presumably behaves in parallel with tissue potassium movements. There is also some evidence for a phosphate depletion syndrome in man characterized by anorexia, weakness, skeletal pain and malaise which can develop with protracted low phosphate intakes, especially if phosphate-binding gels are ingested. /6/

Whether magnesium should also be administered is uncertain, although prolonged parenteral therapy of magnesium-free fluids will undoubtedly result in mild magnesium depletion. However, there is inadequate clinical correlation of symptomatology with serum levels and quantification of body magnesium stores. The adult human body contains about 25 grams of magnesium equally divided between bone and soft tissue. The metabolism

and excretion of magnesium varies with a wide variety of pathologic and physiologic alterations and is only partially related to intake. Average excretion in the urine is 100-200 mg/day on an intake of approximately twice this amount. A minimum requirement for magnesium in man has not been defined, and production of experimental magnesium deficiency by withdrawing magnesium from the diet has been reported only after many weeks of abstinence. Frank deficiency, however, is clearly recognized in animals, especially calves and lambs. The clinical syndrome in man is similar to hypocalcemic tetany but is associated with hypomagnesemia which is alleviated by giving magnesium, but not by giving calcium alone. Muscle tremors, twitching, bizarre movements, delirium, and convulsions may also occur. Reduced levels of magnesium in the serum occur in a number of conditions without overt symptomatology, and subclinical deficiency is difficult to define. While the presence or absence of hypomagnesemia is not a critical diagnostic criteria, serum levels below 1.50 mEq/L should alert the physician to the possible presence of magnesium deficiency. Gastric juice contains approximately 1.0 mEq/L and magnesium deficiency may occur in patients with prolonged gastric suction or with bypass of the small bowel absorptive surface. With prolonged dependence on parenteral fluid therapy, the inclusion of 3 mEq/day of magnesium should be sufficient to maintain magnesium balance, but larger amounts may be needed to replete antecedent deficiency. If hypomagnesemia is documented in association with symptoms possibly due to magnesium deficiency, additional magnesium may be added to the infusion regimen. Magnesium must be given slowly to avoid the vascular dilatation and hypotension associated with hypermagnesemic states.

The need for an intelligent parenteral regimen is intensified if there are exterior losses of body secretions. These might include profuse sweating, or external drainage of saliva, bile, pancreatic fluid, high or low intestinal secretions. The intestinal tract losses are essentially isomolar to plasma, and their replacement is substantially isotonic sodium chloride. Considerations of metabolic alkalosis or acidosis due to intestinal losses has been discussed previously.

A simple schema of replacement of intestinal secretions is shown in TABLE III. The acid-base index is an arbitrary measure of acidity or alkalinity relative to plasma based on

the chloride content. Note that normal saline falls within the range of the acid-base index of gastric aspirate and, hence, virtually all cases undergoing gastric suction can be repleted with saline. Pancreatic secretion is highly alkaline, especially in the case of pancreatic fistulae, while aspirates of the upper bowel are less alkaline due to acid stomach fluid admixture. Despite extensive promotional literature extolling the advantage of solutions whose composition aims to mimic specific intestinal losses, most patients with normal kidney function are able to adjust urinary excretion to compensate for moderate alkalosis or acidosis if only saline is given for replacement. However, in the case where several liters of fluid are being drained or aspirated, it behooves the physician to institute careful collections of all exteriorized secretions, to measure their volume, and to analyze them at least for sodium chloride and potassium. In practice his general principle to follow is — implement judicious replacement of known losses and then give somewhat more than is lost so as to replete previously unrecognized deficits.

#### *References*

1. Barry KG, Brooks MH, Hano JE: The prevention of acute renal failure. In Renal Failure. Philadelphia J. Lippincott Company, 1967, pp 259-271.
2. Watten RH, Cutman RA, Fresh JW: Comparison of acetate, lactate and bicarbonate in treating the acidosis of cholera. Lancet 2:512-514, 1969.
3. Kunin AS, Surawicz B, Sims EAH: Decrease in serum potassium concentrations and appearance of cardiac arrhythmias during infusion of potassium with glucose in potassium-depleted patients. New Eng J Med 266:228-233, 1962.
4. Clementsen HJ: Potassium therapy. A break with tradition. Lancet 2:175-177, 1962.
5. Abbott WE, Krieger H, Holden WD, Bradshaw J, Levey S: Effect of intravenously administered fat on body weight and nitrogen balance in surgical patients. Metabolism 6:681-702, 1957.
6. Lotz M, Zisman E, Bartter FC: Evidence for a phosphorus depletion syndrome in man. New Eng J Med 278:409-415, 1968.

# ACUTE RENAL FAILURE

## Diagnosis, Management, Complications and Prognosis in a War Zone Setting

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Acute tubular necrosis and other nephropathies have contributed to mortality and morbidity in war-related injuries and diseases since accurate medical recording began. During World War II, 40 percent of severely wounded casualties had some degree of acute tubular ischemia at postmortem examination. /1/ In the first year of the Korean War, morphologically detectable tubular necrosis was seen in 18 percent of the autopsies carried out after battlefield deaths.\* Mortality rates among patients with acute renal failure accompanying war-related injury and disease, determined primarily by the severity of the underlying condition and associated complications, have varied from 10 to 90 percent. /1-4/

The management of acute renal failure is challenging and involves meticulous attention to the details of fluid and electrolyte therapy. Development of effective methods of dialysis has provided an additional modality in the treatment of acute renal failure. Its adjunctive value is being evaluated in the combat setting of Vietnam.

The purpose of this report is to present the author's experiences in the treatment of acute renal failure as it occurred in the battle zone environment of the I Corps region of Vietnam while he was aboard the US Navy Hospital Ships SANTUARY and REPOSE from January through October 1970. The diagnostic criteria, etiologic factors, modalities of management, clinical complications and results of the management are presented and discussed. Guidelines for improved methods of treatment are suggested based upon the results of the study.

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*Acute Renal Failure in War Zone - Congo**Method of Patient Evaluation*

In January 1970 a program for the treatment of patients with acute renal failure was instituted aboard the USS Repose. When that ship left Vietnam waters in March, a similar facility was established on the USS Sanctuary. The dialysis unit contained two beds, bed scales, a Travenol® 100-liter Twin Coil artificial kidney and material for peritoneal dialysis. The technical staff included two nurses and four corpsmen trained in the operation of both hemo- and peritoneal dialysis.

Patients were evaluated on admission by the author. Surgical consultations were obtained as indicated. Baseline weights were determined, followed by daily, pre- and post dialysis weights. The following laboratory studies were obtained on a daily basis: complete blood count, blood urea nitrogen (BUN), serum electrolytes, calcium and phosphorus; coagulation studies — prothrombin time, partial thromboplastin time, fibrinogen and platelet count; blood gas studies — arterial pH, pO<sub>2</sub> and pCO<sub>2</sub>. Routine urinalysis was performed on available admission urine as well as electrolyte concentrations and evaluation of the sediment for formed elements. Urinary myoglobin and hemoglobin levels were also determined. Cultures were taken of all wounds, drain sites, sputum, blood and urine on admission, every three days thereafter, and at other times as clinically indicated. Blood cultures were also obtained after each dialysis. Retrograde pyelography was performed when historical factors or physical findings suggested possible obstructive uropathy.

*Nature of Renal Failure*

Twenty-four patients were referred for care during the nine month period described. TABLE I categorizes the 24 patients by sex and national origin. The mean age was 25 years. All but five of the patients were active duty American military personnel. The referring facilities included the major military and civilian hospitals in the I Corps area of Vietnam. TABLE II. The mean time from injury or onset of illness to transfer to the dialysis unit was 4.5 days, ranging from 2 to 9 days. In 19 of the patients renal failure followed trauma; nontraumatic conditions were etiologically related in

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TABLE I  
PATIENT DISTRIBUTION

SEX	TOTAL	24
	Male	23
	Female	1
AGE	MEAN AGE	25
	(2-47 years)	
ORIGIN	MILITARY	22
	American	18
	Vietnamese	3
	Korean	1
	CIVILIAN	2

TABLE II  
REFERRAL DATA

FACILITY	PATIENTS
SANCTUARY	6
85th Evac	4
NSA	3
1st Med.	6
REPOSE	2
Hue Prov.	2
95th Evac	1

five cases. With the exception of two cases with extensive burns, the traumatic injuries were the result of a wide penetrating-combat-missile spectrum. TABLE III. In the nontrauma group, one instance of each of the following conditions was encountered: falciparum malaria, reticulum cell sarcoma with hyperuricemia, methanol ingestion, acute glomerulonephritis and prolonged diarrhea with dehydration and shock.

TABLE IV records the total number of exposures to potential etiologic antecedents of acute renal failure that

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were experienced. Although nearly all patients had received blood, no transfusion reactions were documented. Hypotension of variable severity either at the time of injury or during subsequent surgery, diffuse sepsis, and brief courses of therapy with nephrotoxic antibiotics were common. No cases of obstructive uropathy were discovered.

TABLE III  
FREQUENCY OF ORGAN TRAUMA

Extremities	16
Soft tissue, fractures	9
Multiple amputations	5
Single amputations	2
Bowel	12
Lung	5
Liver	4
Spleen	1
Vascular	5
Kidney	3
CNS	4
Burns	2

TABLE IV  
RENAL FAILURE ANTECEDENTS

Transfusions	17
Hypotension	13
Sepsis	13
Antibiotics	10
Kanamycin, streptomycin, gentamicin, Coly-Mycin	
Congestive heart failure	1
Hyperurcemia	1

Twenty-one of the referrals suffered an oliguric form of kidney failure. There were three patients — all with bilateral amputations of the lower extremities — who presented with rising BUN and serum potassium levels despite urine volume over one liter per day. For those with oliguria, the mean time of onset was three days post injury or illness, with a range of 0-5 days. The average duration of oliguria was 8.5 days with a range of 2 to 15 days. Diuresis failed to occur in any of the patients who expired. TABLE V.

*Acute Renal Failure in War Zone - Conger*TABLE V  
OLIGURIA

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Oliguric	21 patients
Non-oliguric	3 patients
Mean onset post injury	3 days (5-0 days)
Duration (survivors)	8.5 days (15-2 days)
Diuresis (expired)	0 patients
Survival time of those expired	11 days (31-1 days)

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Mean admission laboratory values and ranges are shown in TABLE VI. The low hematocrits occurring in the majority of the patients were the result of blood loss due to trauma and a variety of coagulopathies. Elevated hematocrits were present only in the two burn patients. Elevated white blood counts reflected the septic or stress-hypoxic states in which most referrals arrived. The BUN's were not excessively elevated because of the relatively short periods of shutdown prior to transfer. Hyponatremia was common in both the trauma and nontrauma groups except for those with burns who were hypernatremic. Due to frequent nasogastric suction and intestinal diversion procedures, hypochloremic-hypokalemic alkalosis was nearly as common initially as hyperkalemia with acidosis. Severe acidosis was observed in patients with combined massive trauma and significant hypoxemia from pulmonary complications. As can be seen in TABLE VI, bleeding and clotting abnormalities were frequent. The two major types of disturbance were a diffuse intravascular coagulation most often associated with septicemia, and the factor-deficiency syndrome associated with multiple transfusions of stored blood. The single patient with falciparum malaria developed an isolated thrombocytopenia related to the disease and quinine therapy. Blood gas determinations reflect the high incidence of pulmonary problems. The usual physiologic defect was a ventilation-perfusion imbalance with hypoxia and hypocarbia. The underlying pathology in nearly every case was either severe lung contusion, necrotizing pneumonitis, or the so-called "wet lung syndrome". /5/ Urinary electrolytes and sediment analysis were valuable in assessing the cause of renal dysfunction and in separating those with pre-renal azotemia from those with intra-renal pathology. Seventeen of the 20 patients with oliguria had

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TABLE VI  
ADMISSION LABORATORY VALUES

TEST	MEAN	RANGE
Hematocrit (%)	31	50-19
White blood cells (cu mm)	14,000	2,300-24,300
Blood urea nitrogen (mg/100ml)	73	150-30
Sodium (mEq/L)	130	151-110
Potassium (mEq/L)	4.8	7.4-3.2
Chloride (mEq/L)	89	105-68
HCO <sub>3</sub> (mEq/L)	19	36-6
Platelet count (cu mm)	120,000	32,000-278,000
Prothrombin time (sec)	17	24-13
Partial thromboplastin time (sec)	43	55-35
Fibrinogen (mg/100ml)	150	300-50
pH	7.30	7.50-6.91
pO <sub>2</sub> (mmHg)	83	117-40
pCO <sub>2</sub> (mmHg)	32	43-24
URINE		
Sodium (mEq/L)	38	70-12
(> 20 mEq/L 17 patients) (< 20 mEq/L 5 patients) (Pigmented granular casts: 20 patients)		

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urinary sodium concentrations greater than 20 mEq/L. Detection of typical pigmented casts of acute tubular necrosis on microscopic examination of sediment proved to be the best indicator of frank renal shutdown. These casts were found on urine examination in 20 of the 23 patients. Osmolality studies were of less help because a number of patients had received osmotic diuretics prior to admission.

# MANAGEMENT

Attempts to induce a diuresis were made in nearly every patient, either at the referring facility or shortly after admission to the dialysis unit. TABLE VII. On one occasion diuresis occurred following the use of saline and albumin in a paraplegic patient with unrecognized peritonitis and a perforated gastric ulcer. Using ethacrynic acid, a temporary increase in urine output occurred in two others, but was not sustained despite continued use of the drug. Response to diuretics did not appear to be dose related. Where transient diuresis followed ethacrynic acid therapy, only 25 mg of the drug was given, intravenously. Subsequent trials with higher doses in these patients, and up to 150 mg of ethacrynic acid and 160 mg of furosemide in others, were not successful.

TABLE VII  
ATTEMPTS AT DIURESIS INDUCTION

AGENT	NO. TIMES USED	SUCCESSFUL	TEMPORARILY SUCCESSFUL	UNSUCCESSFUL
Plasma expander	8	1	...	7
Ethacrynic acid	9	...	2	7
Mannitol	7	...	...	7
Furosemide	4	...	...	4

The severity of the complications of renal failure presented by the patient, determined the initial modalities of therapy. Those presenting with pulmonary edema, hyperkalemia or serious neurologic manifestations of uremia

*Acute Renal Failure in War Zone Wounds*

underwent hemodialysis following immediate placement of Quinton-Scribner shunts in an available extremity. A program of fluid, potassium and protein restriction, coupled with high parenteral carbohydrate (occasionally sodium bicarbonate and insulin intake, was initiated in the less critical cases. Kayexalate was used to control serum potassium. Shunting and dialysis were undertaken in these patients when (a) the serum potassium could no longer be maintained below 6.0 mEq/L, (b) the BUN reached a level of 110 to 120 mg/100 ml, (c) there was evidence of progressive wound sepsis and delayed healing, or (d) the overall clinical condition precluded the continued use of the initial conservative program. Periods of hemodialysis varied from four to eight hours, were most often carried out every other day, but frequently daily and occasionally every third day. Regional heparinization, although used initially, was replaced by a system in which the Lee White clotting time was kept in the range of 12 to 15 minutes with small, intermittent doses of heparin, and blood flow rates were maintained continuously at 250 to 300 cc/min. Dialysis was carried out with whole blood, packed RBC or no coil priming depending upon the volume and hematologic status of the patient.

Peritoneal dialysis was used in those patients without marked catabolism who had intact peritoneal membranes. The average duration of this method of treatment was 48 to 72 hours.

In addition to management of the renal failure, intensive therapy was undertaken to alleviate underlying and associated surgical and medical problems. Primarily this involved antibiotics with debridement-drainage procedures for septic complications, hyperalimentation programs to promote wound healing, ventilatory therapy for progressive pulmonary insufficiency, and treatment of coagulopathies.

Increments of blood urea nitrogen were calculated daily for all patients. TABLE VIII. Although there was some overlap, it is evident that the catabolic states of tissue damage and pyrexia increased the rate of rise of the BUN. In septicemia patients with large areas of soft tissue injury, daily increases of BUN were consistently over 45 mg/100 ml. Seventeen of the 23 patients required dialysis. The remainder either did not need dialysis or expired before the manifest clinical indication for it. There were 49 hemodialysis runs

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TABLE VIII  
DAILY INCREMENTS IN BLOOD UREA NITROGEN  
(mg/100 ml)

	MEAN	RANGE
Trauma	28	(62-10)
Non-trauma	12	(31- 4)
Febnile	25	(62-11)
Afebnile	16	(30- 4)

carried out on 12 patients with an average of four dialysis runs per patient. Peritoneal dialysis was used six times on five patients. TABLE IX.

TABLE IX  
MODALITIES OF MANAGEMENT

NO. OF PATIENTS		NO. OF DIALYSES	
Dialysis	17	Hemodialysis	49
Hemodialysis	12	No. per pt. (average)	4
Peritoneal dialysis	5	Peritoneal Dialysis	6
Conservative (No dialysis)	7		

Pre- and post-dialysis laboratory values are shown in TABLE X. In general it can be seen that dialysis was effective in improving metabolic parameters. BUN and electrolyte corrections were intentionally made by small increments in order to avoid neurologic, neuromuscular and cardiac complications. The mean decrement of BUN was 52 mg/100 ml per dialysis. There was considerable variability, however, as can be seen from the table. Ultrafiltration was varied according to the hydration status of the patients, which accounts for the wide range of values. On one occasion urea was added to the bath to retard the rate of urea removal, resulting in a 15 mg/100 ml increase. The situation occurred in a patient who developed seizures following an initial dialysis during which the BUN fell from 200 to 86 mg/100 ml. A second dialysis was required within 24 hours because of recurrent hyperkalemia. Urea was added to the bath to prevent the likelihood of further neurologic manifestations of dysequilibrium. /6/

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TABLE X  
LABORATORY VALUES

TEST	PRE DIALYSIS		POST DIALYSIS	
	Mean	Range	Mean	Range
Blood urea nitrogen (mg/100ml)	119	208.0- 15.0	77	140.0- 15.0
Sodium (mEq/L)	133	141.0-110.0	138	149.0-128.0
Potassium (mEq/L)	5.7	8.5- 3.1	4.0	6.7- 2.7
Chloride (mEq/L)	88	106.0- 64.0	95	106.0- 75.0
HCO <sub>3</sub> (mEq/L)	22	36.0- 6.0	19	24.0- 14.0
Calcium (mg/100ml)	6.2	10.0- 4.1	8.0	9.6- 7.0
Blood urea nitrogen (mg/100ml)	/dialysis		-52.0	-114 to +15
Weight (kg)	/dialysis		-2.0	-4.2 to +0.7

## COMPLICATIONS OF DIALYSIS

There were five instances in which clinical complications were related to dialysis. Two were neurologic with one patient having recurrent seizures, the other progressive lethargy and somnolence. Both were transient and probably resulted from too vigorous dialysis. Fever occurred twice. Once it was thought to be a reaction to blood used in coil priming. On the other occasion, a fever spike with parasitemia developed in the patient with falciparum malaria. This occurred after he had become afebrile and had had negative malaria smears for three days. It was conjectured that the parasitemia was related to the rate of quinine removal with dialysis. Gastrointestinal hemorrhage from unrecognized duodenal ulcers began at the termination of a dialysis run in one patient. His coagulation parameters were normal at the time bleeding was first noted, but a Lee-White clotting time of 20 minutes had been obtained earlier in the run, following a dose of heparin.

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## Clinical Complications

The major clinical complications for all patients from the time of initial management at the referring facility until disposition are shown in TABLE XI. The most frequent problems were related to sepsis and occurred exclusively in the trauma group. Positive blood cultures were obtained in 12 patients with documented septicemia. A single instance of *Pseudomonas* meningitis was associated with *Pseudomonas* septicemia.

TABLE XI  
CLINICAL COMPLICATIONS

Sepsis	51	Gastrointestinal hemorrhage	5
Wound infection	16	Encephalopathies	5
Septicemia	12	Wet Lung Syndrome	5
Pneumonia	7	Acidosis	3
Peritonitis	6	Arrhythmias	1
Abscesses	6	Hemopneumothorax	1
Urinary infections	3	Atelectasis	1
Meningitis	1		

TABLES XII and XIII provide additional data on infectious complications. Other relatively common problems were gastrointestinal and wound hemorrhage, encephalopathies due to metabolic abnormalities, and the "wet lung syndrome". Severe metabolic acidosis with a large anion gap developed in three patients. The onset was acute in each instance and at a time when uremia and acid-base balance appeared to be well controlled with dialysis. Twice an underlying factor of sudden extreme hypoxia was noted, but the onset appeared to be spontaneous in the third instance. Although pyruvate-lactate levels were not measured, it was assumed that lactic acid was the major contributor in the absence of other causes for the acidosis. The lack of renal tubular capacity to respond to the acid load added to the severity of the complication. Improvement was achieved in one instance with sodium bicarbonate and alleviation of the hypoxia. In the other two cases, only partial and intermittent correction was possible despite similar treatment plus dialysis. Digitalis toxicity manifested by paroxysmal atrial tachycardia with variable atrio-ventricular block

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TABLE XII  
INFECTIOUS COMPLICATIONS  
TIME OF ONSET

SITE	NO. OF PATIENTS	
	Present on Admission	Unit Acquired
Wound infections	13	3
Pneumonia	5	2
Septicemia	7	5
Peritonitis	5	1
Abscesses	4	2
Urinary infections	2	1
Meningitis	1	0

occurred on one occasion associated with hypokalemia. A large hemopneumothorax following thoracentesis and massive postoperative atelectasis of one lung following laparotomy occurred in one patient.

Infectious complications were analyzed to determine whether these were present on admission or acquired thereafter, in order to (a) evaluate the unit's contribution to infectious complications and (b) to determine the association between sepsis and the occurrence of renal failure. Infections were considered nosocomial with respect to the dialysis unit if they were either not present on admission, or if alteration in the dominant pathogen cultured from a septic site on admission was demonstrated. The majority of wound infections and most instances of pneumonia and peritonitis were present at the time of admission. Although septicemia, focal abscess formation and urinary tract infections were more often present when the patient was received in transfer, the difference was not significant. The single case of meningitis had developed before the time of admission. Although no causal relationship between sepsis and acute renal failure can be derived from these data, there exists a strong association between the two entities. TABLE XIII.

TABLE XIII gives a breakdown of bacteria cultured from various sites on admission and thereafter. Organisms were considered dialysis-unit acquired if a new dominant organism

TABLE XIII  
INFECTIOUS COMPLICATIONS  
CULTURE DATA

	ORGANISMS*								
	Staph. aur. (coag. +)	Prot. (indole -)	Prot. (indole +)	E. coli	Ps. A	K-E	M-H	A. faec.	Cand
I. Admission									
Total	1	5	7	12	27	17	4	...	...
Wounds	1	4	6	8	14	11	2	...	...
Sputum	...	1	1	3	4	3	2	...	...
Blood	...	...	...	1	6	3	...	...	...
Urine	...	...	...	...	2	...	...	...	...
Sp. fluid	...	...	...	...	1	...	...	...	...
II. Unit Acquired									
Total	1	2	2	3	4	6	4	1	1
Wounds	...	1	1	1	2	...	1	...	...
Sputum	1	...	1	1	1	3	2	1	...
Blood	...	1	...	1	...	3	...	...	...
Urine	...	...	...	...	1	...	1	...	1
Sp. fluid	...	...	...	...	...	...	...	...	...

\* Legend:

Staph. aur. = Staphylococcus aureus  
 Prot. = Proteus  
 E. coli = Escherichia coli  
 Ps. A = Pseudomonas aeruginosa  
 K-E = Klebsiella-Enterobacter  
 M-H = Mima-Herellea  
 A. faec. = Alcaligenes faecalis  
 Cand = Candida

appeared, or if the site was originally sterile or showed normal flora. Polymicrobial infection of all sites except the blood and urine was the rule; however, on three occasions even blood cultures were simultaneously positive for two organisms. The data show that all cultures—whether positive

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at admission or after hospitalization in the unit — grew out gram-negative organisms in all but four instances. Again, regardless of origin, Pseudomonas aeruginosa, Klebsiella Enterobacter and E. coli were the most common bacteria. Proteus was the next most frequent isolate in both groups. Alcaligenes faecalis and Mima-Herellea were never cultured as the predominant or sole organism and were of questionable significance. Staphylococcus aureus was the principal bacterium in one instance of pneumonia and was grown from a biliary drain on another occasion. The sole case of Candida septicemia occurred in a patient with a polyethylene central venous pressure catheter — the tip of which was also found positive for the organism on culture.

RESULTS

Of the 24 patients referred to the dialysis unit, seven survived, 15 expired while in the unit, and two others died subsequently in PACOM facilities following their initial dialysis therapy aboard the SANCTUARY. Of the seven survivors, six regained normal renal function as determined by BUN, serum creatinine, creatinine clearance, urine concentrating and diluting ability, and urinalysis studies. The seventh patient with acute glomerulonephritis attained partial return of renal function with a creatinine clearance of 30 cc/min at the time of discharge, one month post dialysis.

When the survival figures are analyzed on the basis of modality of therapy and type of antecedent illness, the results shown in TABLES XIV and XV are obtained. Of seven patients who did not receive dialysis therapy, four died. Three of the expired patients did not require dialysis at the time of death and one patient expired before its institution. Of the 17 dialyzed patients, four survived and 13 died — 11 while in the dialysis unit and two following transfer. Four of the five patients in the nontrauma group survived. In the trauma group there were three survivors out of 19 patients.

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TABLE XIV  
SURVIVAL - MODALITY OF THERAPY

NO. OF PATIENTS	
Conservative therapy	7
Survived	3
Expired	4
Dialysis therapy	17
Survived	4
Expired	11
Transferred, subsequently expired	2

TABLE XV  
SURVIVAL - ANTECEDENT ILLNESS

Trauma	19	Non-trauma	5
Survived	3	Survived	4
Expired	14	Expired	1
Transferred, subsequently expired	2		

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The causes of death are listed in TABLE XVI. Sepsis --- subdivided into gram-negative bacteremia with septic shock, pneumonia and generalized peritonitis --- was considered the direct cause of death in 11 patients. Infectious processes were a major contributor to demise in an additional four patients. The remaining deaths were due to wet lung syndrome, cerebral edema in a postcraniotomy patient, gastrointestinal hemorrhage and acute hemorrhagic pancreatitis.

TABLE XVI  
CAUSES OF DEATH

Septic shock	8
Pneumonia	2
"Wet lung" syndrome	3
Peritonitis - GI infarction	1
Cerebral edema - medullary compression	1
GI hemorrhage	1
Pancreatitis	1

*COMMENTS*

Acute renal failure constitutes a complex management problem regardless of its etiology and clinical antecedents. In the setting of massive trauma and sepsis, the therapeutic problems are compounded by the necessity for simultaneous treatment of related diseases in addition to the kidney shut-down. Nearly all of the patients treated in this series were suffering from a multiplicity of traumatic injuries. Although extremity wounds were the most frequent, they were often relatively minor in nature. Thoraco-abdominal injuries, and particularly bowel injuries, seemed to be the most devastating

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in terms of patient mortality; they were frequently associated with sepsis and poor wound healing, and necessitated prolonged parenteral feeding.

The etiology of acute renal failure in the trauma group appears to involve a combination of clinical factors. Two thirds of the group had documented hypotension before the onset of renal failure. Nearly all cases received blood transfusions, but without known reactions. Sepsis was an early complication in these patients; however, except in those with septic shock, it was difficult to determine the exact onset of sepsis and its temporal relationship to the kidney shutdown. There were no instances of overt myoglobinuria or hemoglobinuria; urinary tests for these substances were either negative or not significant. Contrariwise, the causal factors in the nontrauma group were more readily explicable and intimately related to the basic disease process as an accepted complication.

Oliguria was a manifestation of renal failure in nearly all patients; but three had urine volumes exceeding a liter per day while there was progressive rise in the BUN and serum potassium. All cases of "high-output" renal failure /7/ occurred in individuals with bilateral amputations of the lower extremities in highly catabolic states. The urine was characterized by low overall solute excretion and a relatively high rate of free water clearance. The urine volume could be further increased with diuretic agents, but there was little effect on solute excretion.

In general, the data from the present experience would indicate that attempts at diuresis with either plasma expanders or diuretics are of little value when there is good clinical and laboratory evidence that oliguria is due to acute tubular injury. Often the immediate critical problem at the time of admission was overhydration, resulting from unsuccessful fluid trials to "flush the kidney".

The treatment of acute renal failure, as an isolated aspect of the total disease process, was successful in that none of the patients expired as a direct result of a renal metabolic complication. This is not to say, however, that further improvement in dialysis techniques and metabolic management could not provide further benefit in treating the basic disease and its complications. Though controlled studies

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are lacking, it would appear that patients tend to feel better and recover more often with early and frequent dialysis designed to restore approximate biochemical normalcy. The survival data fail to indicate that early dialysis significantly altered the ultimate outcome, but the time from onset of renal failure to death was possibly somewhat longer in those expiring.

A disappointing observation was that vigorous ultrafiltration with several kilograms of fluid removal was not beneficial in reversing the "wet lung" process once it was established. Interstitial and alveolar edema fluid seemed to remain fixed regardless of weight loss or the addition of mannitol or albumin to the patient's vascular volume.

Technical difficulties encountered were mainly those of hypotension both in the early and late phases of dialysis, the finding of adequate shunt sites in those with multiple extremity injuries, and occasional clotting of the coil or venous tubing when attempting to keep the degree of anticoagulation at a minimum. None of these constituted an insurmountable problem and both standard and innovative measures could be applied to alleviate them. Whether regional heparinization should have been used more frequently in the trauma patients is uncertain. Bleeding was not an overall significant problem; however, in one patient with multiple unsuspected duodenal ulcers, who bled massively following dialysis, hemorrhage was the direct cause of death.

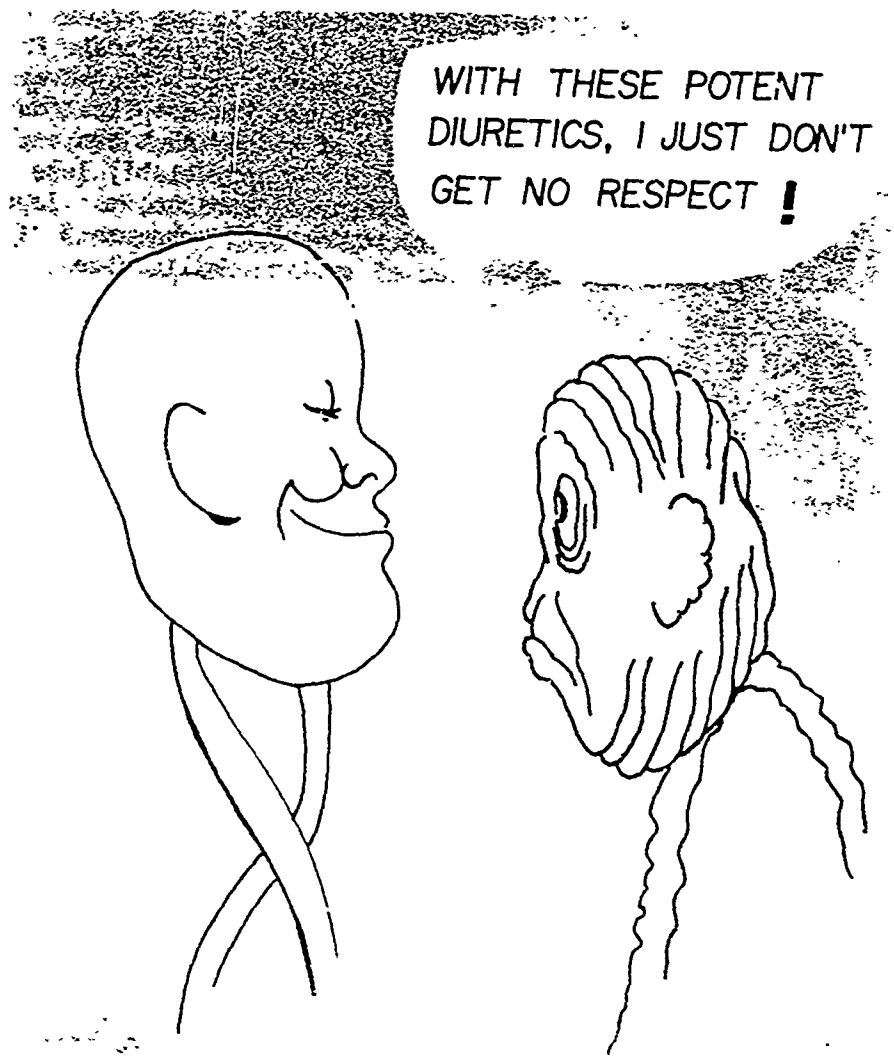
The major clinical problem and primary prognostic indicator was the presence of sepsis. It was extremely difficult to reverse the process, and once septicemia, severe pneumonitis, peritonitis or progressive wound infection developed, there seemed to be little of therapeutic benefit available. No doubt the frequency of virulent gram-negative organisms was a significant factor. The disc sensitivity and tube-dilution studies performed on initial cultures suggested that the *Pseudomonas*, *Klebsiella-Enterobacter*, *E. coli* and *Proteus* bacteria should have responded to the appropriate antibiotics — including kanamycin, gentamycin, chloramphenicol, ampicillin and cephalothin — even when appropriate adjustments in dosage both for dialysis and decreased renal function were made. /8,9/ An additional possibility may be that more vigorous and early surgical debridement, drainage and amputation should be carried out, in view of the overall disappointing results in cases presenting infectious complications.

# *Acute Renal Failure in War Zone - Conclusions*

Overall survival of this group of patients was 29 percent with all but one of the deaths occurring in the trauma group. It is evident from this experience that the prognosis for patients with acute renal failure depends upon the severity of the underlying trauma or illness and its complications. Though the metabolic consequences of kidney shutdown could be controlled, the mortality rate was not appreciably less than that noted with pre-dialysis methods of management. Improved survival rates will have to await improved management of the basic injuries and prevention of septic complications.

## *References*

1. Smith LH, Jr, Post RS, Teschan PE, et al: Post-traumatic renal insufficiency in military casualties. II. Management, use of artificial kidney, prognosis. Surgical Research Team. Army Medical Service Graduate School, Washington, D.C. February 1955.
2. Teschan PE, Post RS, Smith LH Jr, et al: Post-traumatic renal insufficiency in military casualties. I. Clinical characteristics. Amer J Med 18:172-186, 1955
3. Proceedings of Study Group on Acute Renal Failure. US Army Surgical Research Unit, Brooke Army Medical Center, Fort Sam Houston, Texas. Symposium, October 14-16, 1957
4. Shelton A, Donadio JV Jr: Post-traumatic acute renal failure in Vietnam. A comparison with the Korean war experience. John Hopkins Med J 124:95-105, 1969
5. Ashbaugh DG, Petty TL, Bigelow DB, et al: Continuous positive-pressure breathing in adult respiratory distress syndrome. J Thorac Cardiovasc Surg 57:31-41, 1969
6. Peterson CP, Swanson AG: Acute encephalopathy occurring during hemodialysis. Arch Intern Med 113:877-880, 1964
7. Shreiner GE: In Renal Disease. Black DAK (ed). Philadelphia: FA Davis Company, 1967, p 310
8. Kunin CM: A guide to the use of antibiotics in patients with renal disease. A table of recommended doses and factors governing serum levels. Ann Intern Med 67:151-158, 1967
9. Gingell JC, Chisholm CD, Calnan JS, et al: The dose, distribution and excretion of gentamycin with special reference to renal failure. J Infect Dis 119:396-401, 1969



## RECENT ADVANCES IN THE IMMUNOLOGY OF GLOMERULONEPHRITIS

MAJ Stephen R. Steinmuller, MC

In 1827 with his description of a heterogenous group of patients having "albuminous urine" and renal insufficiency, Richard Bright established chronic renal disease as an entity and provided an eponym for a large group of disorders affecting the kidneys. By 1836, Bright had collected some 100 cases which he presented in tabular form in the Guy's Hospital Reports of that year. The common denominator of these findings was albuminuria associated with gross morphologic changes in the kidneys at postmortem. It is probable that the majority of these patients were suffering from chronic glomerular diseases.

Little progress was made in the delineation and understanding of these diseases until the systematic work by Volhard and Fahr in 1914 in which inflammatory processes of the glomerulus were separated from conditions which were thought to be either primarily vascular or degenerative in origin. Since then classification and understanding of glomerulonephritis has remained primarily descriptive either from a clinical or a pathological standpoint. A lack of information concerning either etiology or pathogenetic mechanism has made other approaches impossible. The outstanding contributions of authors such as Addis, Ellis, Jennings and Earle, Longcope, and others were concerned with the clinical and pathological correlations of a group of diseases whose origins remained a mystery. In the 1950s and 1960s with the development of corticosteroids and antimetabolites as potential therapy, the lack of fundamental knowledge of these illnesses became more critical.

Appreciating the deficiencies of the clinical approach, a number of workers began in the 1930s to develop experimental models of human glomerulonephritis in laboratory animals. Many of the inherent limitations of human study could thus be bypassed, allowing great latitude in the manipulation of experimental material. Thus, beginning in earnest in 1933 with the work of M. Masugi utilizing poorly understood immune

mechanisms to produce clinical and pathological disease states indistinguishable from human glomerulonephritis, a new concept of the pathophysiology of glomerular injury has evolved. Although many details remain unclarified and etiologic factors are still largely unknown, the progress to date has been sufficient to create a new basis for the classification and possible treatment of glomerulonephritis.

#### EXPERIMENTAL MODELS

Great effort has been expended in the development and understanding of models of immunologic glomerular injury. It has become evident from such study that two mechanisms are operative in experimental and human disease states the first mediated by an antibody assault formed and directed specifically against constituents of the glomerular basement membrane (GBM), and the second caused by circulating soluble immune complexes (i.e. antigen-antibody complexes unrelated to glomerular tissue) passively lodging within the glomerulus leading to injury of this innocent bystander. Application of these concepts of pathophysiology to human disease is impossible without familiarity with the animal models from which they have been developed.

#### Nephrotoxic Nephritis: The Masagi, Steblay and Kay models

(Reference: Good RA et al. *Fed Proc* 28:191-205, 1969)

Working in 1933, Masagi was able to show the development of glomerulonephritis in rats injected with serum from ducks or rabbits immunized against rat kidney antigens. The character and severity of the resulting disease was related to the strength and dosage of heterologous serum used and both acute and chronic nephritis were produced. Figure 1. In this model large doses of heterologous serum led to early heavy proteinuria, and subsequent development of the nephrotic syndrome, renal failure, and death weeks or months after. Smaller doses caused lesser degrees of proteinuria with the gradual development of a chronic glomerulonephritis. In both instances, renal morphology in the initial phase consisted of swelling and proliferation of endothelial cells, basement membrane thickening, and occasional fibrin thrombi. Later there was

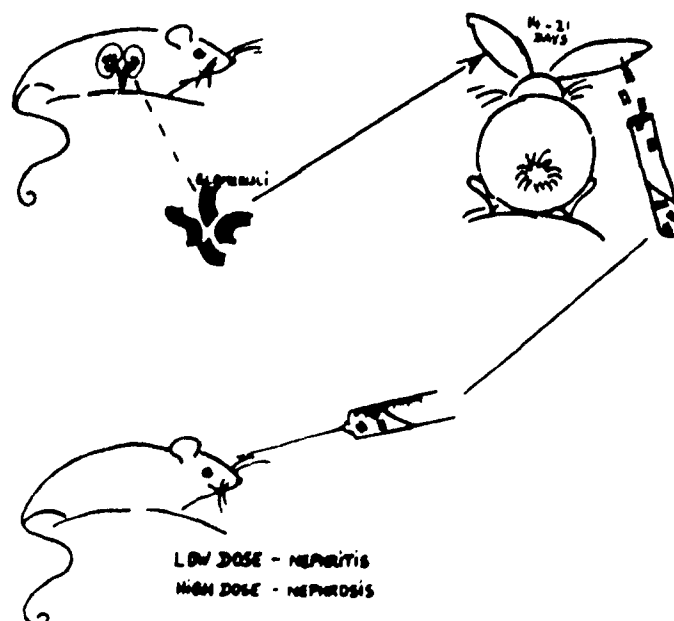


Fig. 1.

Masugi model. Kidney from rat is injected into rabbit to develop antikidney antibody. This is directed mostly against the rat kidney basement membrane. Injection of rat with antikidney antiserum from the rabbit produces nephrotoxic nephritis which is based on an immunological assault directed against the glomerular basement membrane. The renal disease may be either acute nephrotic syndrome or chronic nephritis, depending on dose or potency of the antikidney antibodies given. (Good, Fig. 7.) Reproduced with permission.

progressive thickening of glomerular basement membranes with endothelial and epithelial proliferation, lobulation of tufts, the formation of adhesions and fibrous scars with gradual obliteration of the glomerulus.

In the Kay model (Figure 2) nephrotoxic serum was produced in the duck by injection of rabbit kidney antigens. In this case injection of the serum into rabbits was followed by a 6-8 day period without proteinuria or morphologic change after which heavy proteinuria and glomerulonephritis developed.

Analysis by several groups has established the salient features of these models. The toxic effect of the heterologous serum lies in the presence of antibodies directed against basement membrane antigens. Moderate doses lead to immediate fixation of antibody on basement membrane sites of the target glomeruli. This is followed by a sequence of complement fixation and activation, chemotactic attraction of polymorphonuclear leukocytes by a C567 complex and perhaps liberation of lysosomal enzymes. Depletion of animals of either polymorphonuclear leukocytes or complement averts both

*Immunology of Glomerulonephritis* Steinmuller

the early morphological changes and the immediate proteinuria. In the Kay model the fact that duck gamma globulin fixes rabbit complement poorly explains the lack of immediate toxicity despite antibody fixation. When larger doses of antibody are administered, leading to saturation of most of the antigenic sites, proteinuria develops even in complement and polymorphonuclear leukocyte depleted animals. The reason for this is unknown.

Dixon's group have also shown that following this initial period of injury there occurs an autologous phase with the development of host antibodies directed against the heterologous antibody fixed within the glomeruli. Fixation of these newly formed antibodies to GBM-bound heterologous antibody results in sustained nephritis and explains the delayed appearance of disease in the Kay model. Elimination of this host response by x-radiation or neonatal induction of tolerance to foreign gamma globulin prevents this autologous phase, permitting gradual healing of the initial phase glomerular lesions.

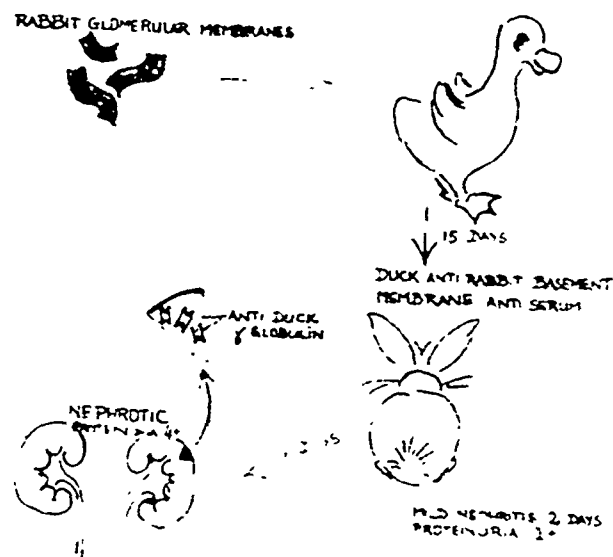


Fig. 2

Kay model: Antibody against rabbit glomerular membranes is formed in the duck. Small dosage of duck antirabbit kidney serum injected into rabbit. Rabbit complement is poorly fixed by duck antibody. The rabbit forms antibodies against duck gamma globulin some of which is fixed to its glomerular membrane. A different form of directed immunological assault may ensue where for one reason or another foreign antigen is attached to host glomerular membrane when antibody against that antigen becomes available (Good Fig. 11). Reproduced with permission.

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Although the intensive study of the Masagi and Kay models has permitted significant insights into the mechanisms of renal injury caused by anti-GBM antibodies, it was not until Steblay's demonstration of the induction of autologous anti-GBM disease in sheep in 1962 that applicability of these models to forms of human glomerulonephritis became established. The Steblay model (Figure 3) consisted of the injection of heterologous glomerular basement membranes isolated from other species, combined with Freund's complete adjuvant, into sheep. Animals thus treated invariably developed a fulminant glomerulonephritis terminating in death within weeks to months. The pathology in these cases was remarkably similar to human rapidly progressive glomerulonephritis, showing prominent epithelial cell proliferation with fibro epithelial crescents formation and glomerular obliteration. The disease was transferable to healthy animals by either cross-circulation or the injection of serum from nephrectomized diseased animals. In the latter case Dixon's group has shown a sharp rise in the level of circulating autologous anti-GBM antibodies once their site of removal (the kidney) is eliminated. These investigators have recently demonstrated similar rises in antibody titers in the sera of certain nephrectomized patients awaiting transplantation.

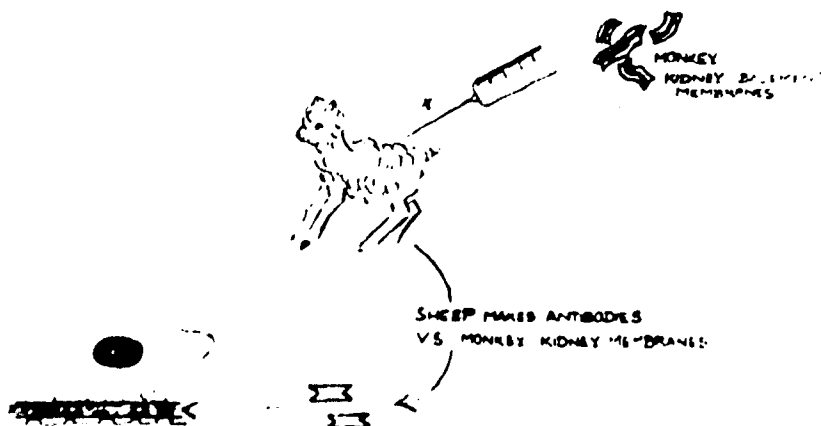


Fig. 3

Steblay model. Isolated basement membranes from a primate or human source are injected into the sheep. The sheep makes antibody against these foreign membranes which cross-react with antigens on the sheep's own glomerular membrane. Thus, a directed immunological assault occurs against the sheep's glomerular membranes by an autoantibody formed in the sheep. The disease produced is a fatal progressive nephritis. (Good, Fig. 8) Reproduced with permission.

The demonstration that the immunization of sheep to heterologous glomerular basement membrane antigen causes the formation of antibodies having cross-reactivity to autologous antigens led several workers to investigate the possibility of immunizing animals to homologous and autologous glomerular antigens. These efforts were surprisingly successful in a number of hosts, which led to the production of true autoimmune anti-GBM nephritis.

Analysis of the histopathology of all these models of nephrotoxic nephritis by immunofluorescent techniques reveals intense staining for IgG and B<sub>2</sub>C in a linear, ribbon-like pattern along the glomerular basement membranes (Figure 4). By extensive investigation the specificity of the histochemical techniques used and the pathogenic significance of the linear deposition of immunoglobulins have been well-established. This pattern may now be considered the hallmark of direct immunologic assault on the glomerulus.

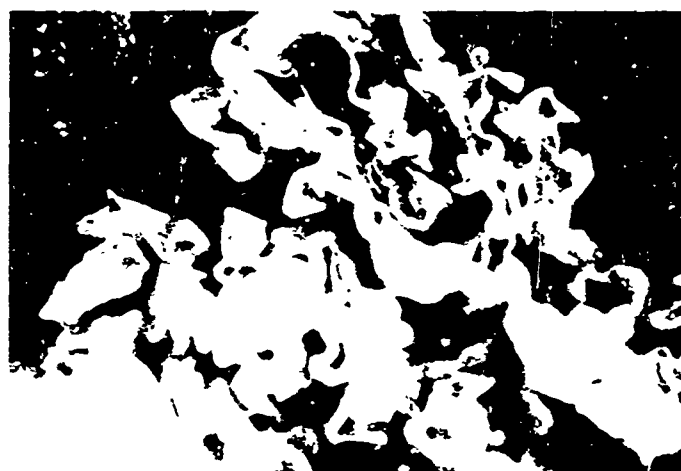


Fig. 4. Fluorescent photomicrograph of a diseased glomerulus stained with fluorescence-labeled anti-globulin to IgG. Note the ribbon-like pattern corresponding to the deposition of immunoglobulin in the Masugi, Kay, and Steblay models.

# Immunology of Glomerulonephritis Stemmuller

## Immune Complex Disease The serum sickness, Heyman, and other models

### Serum Sickness Model (acute and chronic)

The injection of foreign proteins into animals or man has been repeatedly shown to result in the typical syndrome of serum sickness, manifested by fever, arthralgia, arteritis and glomerulonephritis. The pathogenesis of the syndrome has been clearly delineated by several investigators. Figure 5. The injected antigen elicits an antibody response after a variable period, usually within 14 days. As increasing amounts of antibody are produced, complexing of antibody with antigen occurs within the circulation. Complexes formed early in the course under states of antigen excess tend to be soluble since the amounts of antibody available are too small to form macromolecular precipitating aggregates. These circulating soluble complexes are biologically active in fixing and activating the complement system and other mediators of increased vascular permeability. These changes appear necessary for the subsequent deposition of the complexes within glomerular capillary loops and vessel walls. Finally, complement activation in situ

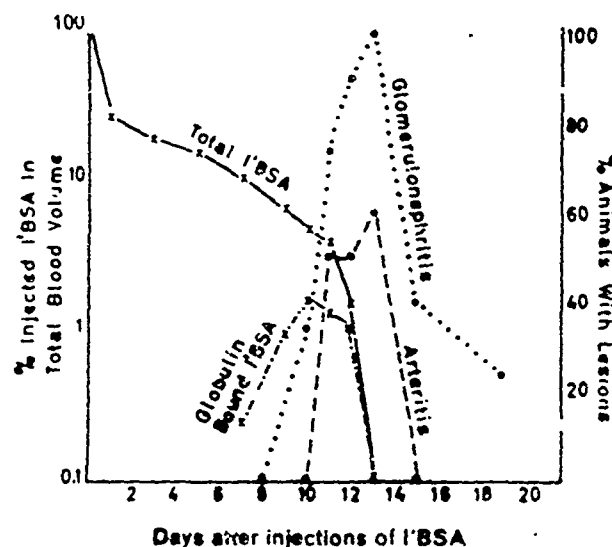


Fig. 5. Classic picture of serum sickness as revealed by immunochemical analyses of Dixon and co-workers. Note that the arteritis and glomerulonephritis begin while soluble antigen-antibody complexes are present in the circulation just prior to the onset of immune elimination. BSA-bovine serum albumin. (Good, Fig. 1., as taken from Dixon J J Arch Path 65 20, 1958, Fig. 2.) Reproduced with permission

by deposited immune aggregates initiates the injurious inflammatory response (vide infra). Thus, the appearance of glomerular and arterial lesions closely parallels the development of the antibody response and the subsequent disappearance of circulating antigen, as complexes are deposited within blood vessels or are cleared by the reticulo-endothelial system. Free antibody first becomes detectable in the circulation at the time of disappearance of antigen, reaching a peak level three days later. Small amounts of antibody are subsequently produced and the serum level falls as normal immunoglobulin catabolism takes place. The resulting glomerulonephritis is short-lived, corresponding to the period during and shortly after antigen removal. Pathologically there is a marked proliferation of endothelial cells with encroachment on capillary lumina and diffuse swelling of the glomerulus. Polymorphonuclear leukocyte accumulation is seen at the sites of tissue injury. By immunofluorescent techniques (Figure 6) antigen, antibody, and B<sub>1</sub>C globulin (C<sub>3</sub> - the third component of complement) are seen deposited in a granular, lumpy-bumpy fashion along the basement membrane. Early in the course, electron microscopy reveals occasional deposits along the endothelial side of the basement membrane while later study shows large electron dense "humps" along the epithelial surface. These are believed to represent large macromolecular aggregates of antigen antibody complexes. Proteinuria is a prominent result of the tissue injury but rapidly clears with morphologic healing following disappearance of circulating complexes. Proof of the central role of these protein aggregates in the pathogenesis of the disease is given by the prompt development of identical lesions in animals injected with soluble immune complexes created in vitro.

With more complete understanding of acute serum sickness in the 1950s, efforts to produce chronic disease states by prolonging the phase of antigen excess were initiated. Dixon and co-workers and later Germuth and associates were able to produce chronic glomerulonephritis in rabbits through repeated injections of foreign antigen over periods of weeks to months. In such experiments, animals could be divided into three groups depending upon the degree of their antibody response. Animals developing extremely high titers of antibody were able to maintain states of antibody excess within the circulation despite increasing doses of antigen. Under these circumstances precipitating insoluble complexes were formed and were rapidly cleared by the reticulo-endothelial system. Glomerulonephritis,

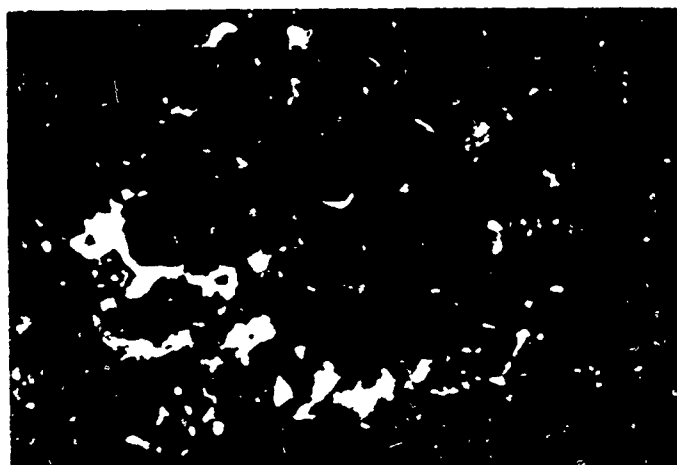


Fig. 6. Fluorescent photomicrograph from animal with acute serum sickness. Note the lumpy-bumpy pattern of fluorescence from IgG + B<sub>1</sub>C which is characteristic of acute serum sickness-type glomerulonephritis.

occurring after the initial exposure to antigen, quickly cleared and chronic disease did not develop. Anaphylaxis was a common sequel of antigen injection. A second group of animals failed to produce any antibody and did not show renal injury. Animals producing average or low levels of antibody, however, developed progressive glomerulonephritis. In this group states of antigen excess could be obtained repeatedly with antigen injection and soluble immune complexes were present for prolonged periods. The renal disease was manifested by hematuria, proteinuria, azotemia and frequently death. The nephrotic syndrome was a common feature. The earliest morphologic change was pronounced diffuse thickening of basement membranes, followed by proliferation of endothelial and epithelial cells, lobulation and scarring of capillary tufts, with subsequent obliteration by collagenous tissue. By immunofluorescent techniques antigen, antibody, and B<sub>1</sub>C were deposited together in the same granular, lumpy fashion as in acute serum sickness. Extent of deposition was related only to the degree of basement membrane change, and in no case could either antigen or antibody be demonstrated alone, without the other. By electron microscopy dense sub-epithelial deposits were noted within the basement membrane with sheets of epithelial cell cytoplasm over them. The size and distribution of these dense "humps" corresponded closely to the deposits seen by immunofluorescence.

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To determine reversibility of disease once established, Dixon's group followed a number of rabbits with mild to severe proteinuria and morphologic change at biopsy for a variable period after cessation of antigen injections. In those animals with the most pronounced histologic change and heaviest proteinuria, scarring and destruction proceeded relentlessly to renal failure. When only mild proteinuria was present in association with early morphologic change, proteinuria decreased or disappeared after cessation of antigen injection. At sacrifice or death little morphologic improvement could be seen even in animals with clinical evidence of healing. Immunofluorescent staining for antigen and B<sub>1</sub>C was progressively less intense, however, and breaking up of the subepithelial dense deposits could be seen by electron microscopy. Thus, these studies demonstrated a "point of no return" beyond which healing could not occur, and showed that histologic healing when it occurred lagged far behind clinical and immuno-histochemical changes.

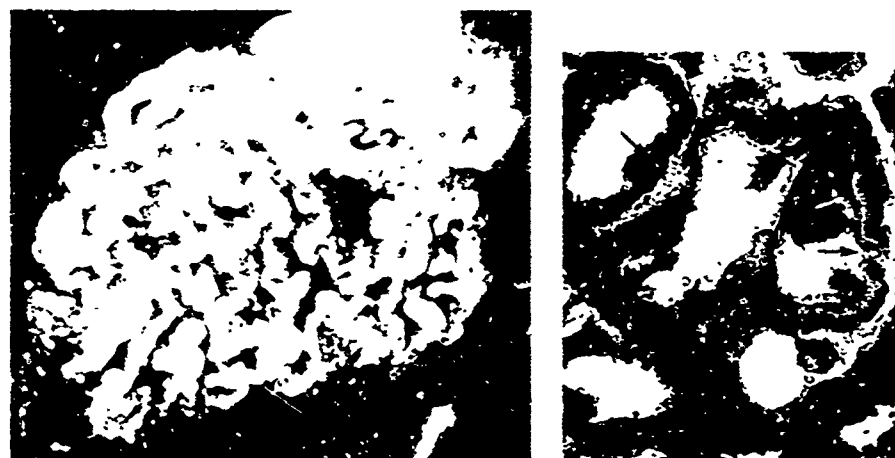
*The Heyman Model*

In 1959 Heyman and co-workers reported the results of a series of experiments involving the production of the nephrotic syndrome in rats by the intraperitoneal injection of rat kidney extracts and Freund's adjuvants. The severity of the disease appeared to be related to the dose injected. When extracts of liver, muscle and lung were used with adjuvant disease was seldom produced. Additionally, Freund's adjuvant alone or rat kidney suspension alone were ineffective. The disease, once started, continued despite cessation of the injections; and at autopsy moderate to severe membranous glomerulonephritis with focal interstitial plasma cell and lymphocyte infiltration were seen.

Although this model was initially thought to be analagous to the Steblay model, subsequent investigation revealed that IgG and B<sub>1</sub>C were deposited in the glomeruli of affected animals in a granular, lumpy-bumpy fashion in contrast to the linear pattern of anti-GBM nephritis. Figure 7. Electron dense subepithelial deposits like those of chronic serum sickness, were noted corresponding presumably to aggregates of antigen-antibody complexes. Figure 8. The final isolation of the specific renal tubular antigen involved allowed the characterization of the pathophysiology of this model. Injection of complete Freund's

*Immunology of Glomerulonephritis - Steimuller*

adjuvant combined with a purified high density lipoprotein obtained from the brush borders of proximal tubular cells was shown to lead to production of auto antibodies which then reacted with both the injected antigen and the minute quantities of autologous renal tubular antigen. As in the serum sickness models, complexes were deposited with complement in the glomeruli of the affected animals, leading to proteinuria and nephritis. The disease was self-perpetuating because of the normally occurring continuous liberation of renal tubular antigen into the animal's circulation. The elimination of the normal state of tolerance to this autologous circulating antigen by immunization thus produced a progressive glomerulonephritis through passive accumulation of antigen-antibody aggregates within the glomerulus. The applicability of this model to human and animal autoimmune states is obvious.



**OTHER MODELS**

Persistent lymphocytic choriomeningitis viral infection in mice

Fig. 7 (left). Fluorescent photomicrograph of the kidney in the Heyman model. The granular pattern of IgG and B<sub>1</sub>C deposition corresponds to subepithelial immune complex deposits.

Fig. 8 (right). Portion of glomerular tuft. There is diffuse irregularity in the subepithelial aspect of the glomerular basement membrane with many dense deposits present. Intervening projections of the lamina densa are seen, which are noted at times to surround the deposits (arrow on the left). In one focus (arrow on the right) clear areas are noted in the basement membrane. (Rosen, Fig. 5.) Reproduced with permission from publisher, W.B. Saunders Co., and author. Photograph reduced from figure which showed magnification  $\times 3100$ .

Certain mouse strains injected shortly after birth with lymphocytic choriomeningitis virus (LCM) carry the virus throughout life making low levels of anti-LCM antibody. Different strains vary in the amount of virus present, and in

the time and extent of their antibody response. Mice having least amounts of virus and antibody do not develop nephritis while those with the highest levels show the early development of chronic disease. Within the glomeruli, antibody, complement and virus particles can be shown deposited together in the classic granular, lumpy-bumpy pattern. Gamma globulin eluted from these kidneys readily binds LCM virus, and circulating IgG-virus complexes can be detected in the serum of diseased animals. These findings would seem to establish the process as an immune complex mediated nephritis.

#### Auto immune disease of New Zealand mice

Certain strains of New Zealand mice have been found to develop an auto immune illness comparable to human systemic lupus erythematosus. The disease appears earlier and is more severe in females, and is characterized by hemolytic anemia, glomerulonephritis and antinucleic acid antibodies. The nephritis appears in large measure related to deposition of DNA complexes and anti-DNA antibodies. The importance of latent infection with murine leukemia virus in contributing to the development of disease is currently being investigated. The finding of virus like particles within cells from patients with SLE make this model attractive for further understanding of its human counterpart.

#### Additional Aspects of Immunological Injury

Role of antibody characteristics, complex size, complement, the coagulation process and mediators of increased vascular permeability

Deposition of immune complexes with resulting disease appears to occur only in special circumstances. Complex solubility is important and relates to antibody characteristics and circumstances of formation. In the case of precipitating antibodies, complex solubility occurs only when formation takes place with antigen in slight excess, leaving antigenic sites unsaturated. In certain circumstances, however, non precipitating antibodies are formed, making the relative concentrations of antigen and antibody unimportant. In this case size also appears less important. Under most conditions complexes of less than 19S in weight do not localize in blood vessels and glomeruli; however, in the case of non-precipitating

antibody complexes of intermediate weight circulating for prolonged periods will localize in glomerular basement membranes.

The role of complement in the various forms of experimental nephritis has been extensively investigated. In the case of nephrotoxic anti-GBM nephritis complement activation is an integral part of the pathologic process. Immediate proteinuria after antibody fixation to glomerular antigen is related to the chemotactic properties of activated  $C_3$  and to a  $C_567$  complex. The resulting polymorphonuclear cell accumulation is essential and, as mentioned earlier, depletion of animals of either complement or polymorphonuclear leukocytes prevents immediate glomerular injury except when large doses of antibody are used.

In immune complex disease complement is necessary for the genesis of arteritic lesions but not for the development of glomerulonephritis. Complex deposition in vessel walls or glomerular capillary loops results from changes in vascular permeability mediated by release of vasoactive amines. In the rabbit, platelets are the major reservoir for these amines and their release in serum sickness is dependent on elaboration of a humoral substance from a specific mononuclear cell interacting with antigen. Treatment of animals with antihistamines has been shown to prevent both deposition of complexes and development of glomerulonephritis. The role of complement in complex disease lies only in the production of arteritis by chemotactic attraction of polymorphonuclear cells and subsequent release of tissue damaging lysosomal enzymes. That this mechanism is not part of the glomerular injury is shown by the development of glomerulonephritis of identical morphology and severity in complement depleted animals.

Since 1940 evidence has been accumulating which implicates the coagulation process as the mediator of much of the tissue injury in glomerulonephritis. Working with the Masugi model of acute glomerulonephritis, researchers have repeatedly shown remarkable prevention of morphologic changes by the use of either heparin or warfarin. Endothelial cell proliferation and swelling, crescent formation, necrosis and sclerosis are all abolished by these forms of therapy. Interestingly, proteinuria is unchanged or more severe in treated animals. More recently the same protective action has been shown for acute immune complex disease through use of either heparin, warfarin or urokinase. By immunofluorescent techniques in untreated animals fibrin and fibrinogen derivatives can be found within

endothelial and mesangial cells as well as within the urinary space. More severe cases demonstrate crescent formation. The distribution of this material differs from that of IgG which is deposited only along basement membranes. Treatment abolishes only the staining for fibrinogen derivatives and not IgG. Similar staining and morphologic changes can be caused by nonimmune mechanisms, i.e. induced intravascular coagulation. In all cases studied with electron microscopy, fully polymerized fibrin can occasionally be demonstrated either within the capillary space or in endothelial cells. More commonly, various forms of incompletely polymerized fibrin (fibrinoid) are seen along the basement membranes and within mesangial and endothelial cells. The toxicity of these substances is presumed to be related to both inefficient breakdown by phagocytizing cells and interference with the vascular supply. As mentioned before, the more severe cases show such material within the urinary space in association with fulminant crescent formation. The fact that several different forms of anticoagulation are successful in aborting these pathologic changes suggests that their protective action is mediated through inhibitions of the coagulation system not by some other mechanism, e.g. anticomplementary effect or antiinflammatory effect. All this information speaks for the coagulation process as the primary cause of the proliferative and sclerosing lesions of most forms of glomerulonephritis. Although proteinuria is not prevented by anticoagulant treatment in Masugi nephritis it is eliminated in induced intravascular coagulation nephritis and in immune complex disease in mice. These observations suggest possible differences in the causes of proteinuria between anti-GBM disease and immune complex disease.

Unfortunately the proximate events leading to coagulation within nephritic glomeruli are unknown. Ag-Ab complexes have been shown to accelerate the coagulation process *in vitro*, probably through an effect on platelets. Yet actual initiation of the coagulation process has yet to be demonstrated for either immune complexes or for tissue bound antibody. More investigation is needed in this important area.

#### APPLICATIONS OF EXPERIMENTAL NEPHRITIS TO HUMAN DISEASE

Techniques developed in the understanding of experimental models have proven extremely valuable in the study of human

glomerulonephritis. The immunofluorescent examination of renal biopsy specimens and the use of methods for the elution of antibody have allowed identification of most forms of glomerulonephritis as either anti-GBM disease or immune complex disease. Although the basic causes of the alterations in immunity remain unknown, certain aspects of human glomerular injury are now clear.

#### Anti-GBM Disease

Goodpasture's syndrome and rapidly progressive glomerulonephritis (RPGN), two uncommon forms of nephritis, have repeatedly been shown to be associated with deposition of antiglomerular basement membrane antibodies in a linear fashion with complement. The finding of fibrin and fibrin degradation products within the glomerular capillaries and cells is presumed to be the cause of the marked cellular proliferation leading to a rapidly fatal clinical course. Figure 9. That antibodies eluted from diseased kidneys produce fulminant Masugi type nephritis when injected into primates establishes their pathogenicity. When patients with these diseases are nephrectomized prior to transplantation these antibodies rise in titer in the circulation. Subsequent placement of healthy renal tissue in these patients with high antibody titers has been shown to result in the disappearance of circulating antibody concomitant with the development of disease in the transplanted kidney. At biopsy or postmortem IgG is again seen deposited in linear fashion along the basement membranes associated with the expected histology. In view of these facts it has now become accepted practice to wait for the gradual disappearance of circulating antibody over periods of months before considering transplantation.

Some differences in the specificity of auto antibodies from these two diseases have been described. Thus IgG from kidneys of patients with Goodpasture's syndrome appear to have greater reactivity with other renal and non-renal antigens as well as with glomerular antigens from other species. In contrast, antibody from RPGN kidneys shows little reactivity with renal tubular antigens and alveolar basement membrane antigens, and is far more species specific. These findings help explain the differences in pulmonary involvement despite identical renal histology and course.

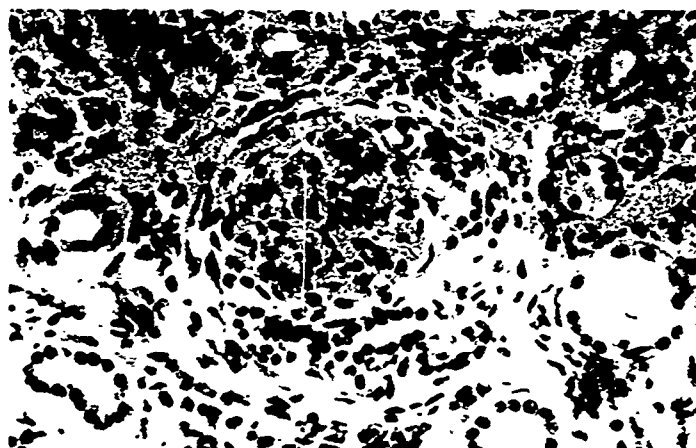


Fig. 9. Renal biopsy from a patient with rapidly progressive glomerulonephritis (RPGN). Note the profound crescent formation.

Of great practical interest are the possible reasons for the development of this auto-immune assault on the glomerulus. Although antigens having immune cross reactivity with GBM have now been identified in normal human serum and urine, their role, if any, in the development of nephritis is unknown. The experimental demonstration that rabbits may be sensitized to similar antigens from their own urine is encouraging evidence for a pathogenic role for these substances. Nevertheless it would appear likely that some infectious process is also involved in this alteration in immunity. At present there is no available information on this point. Although antigenic cross reactivity between nephritogenic streptococci and human GBM has been demonstrated, the lack of evidence of preceding streptococcal infection in most cases of human anti-GBM nephritis and the fact that post streptococcal acute glomerulonephritis appears to be an immune complex disease speak against an etiologic role for these organisms.

#### Immune Complex Disease: Poststreptococcal glomerulonephritis (PSGN)

Despite rather complete knowledge about the inciting organism in post streptococcal glomerulonephritis (PSGN), the full pathogenic sequence leading to acute glomerular inflammation remains to be demonstrated. Nephritogenic streptococci are readily cultured and have been studied extensively with regard to capsular antigens. Organisms with lancefield group A capsular polysaccharide and specific types of M protein (1, 4, 12, 25 and 49) (red lake) are now known to be nephritogenic. In addition opsonins directed against these M proteins are responsible for type specific immunity preventing reinfection.

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The sequence of infection, followed by a latent period and nephritis associated with rising titers of antibodies to various streptococcal antigens and a fall in serum complement, strongly suggests an immunologic basis for the illness. Efforts to document this impression have met with varied success. Lange et. al. in 1966 reported that all cases show the presence of IgG and B<sub>1</sub>C in a granular distribution along the glomerular basement membrane. The majority of investigators have found these proteins in most but not all cases, again in a granular, lumpy distribution. By electron microscopy dense deposits are found along the subepithelial surface of the basement membrane in all cases which by ferritin conjugated antibody techniques are composed of IgG plus B<sub>1</sub>C presumably linked to an unknown antigen. Additionally, dense deposits have been reported in the subendothelial area, between endothelial cells and within the capillary lumen. These deposits appear to contain IgG and B<sub>1</sub>C while fibrinogen derivatives are also suggested.

Efforts to complete this pathogenetic puzzle by demonstrating streptococcal antigen within glomeruli have until recently been rather unsuccessful. Michael et. al. were able to show such proteins in only two of ten patients, while Segal and co-workers reported finding streptococcal antigen in six of ten cases. Recently, Tresar and associates have shown by very elegant study such antigen in all cases of this disease. The antigen is a lipoprotein of 120,000 molecular weight contained in the plasma membrane of nephritogenic streptococci but not in other bacteria. Within the first few days of onset of disease antigen is distributed in the glomerulus in the same fashion as IgG and B<sub>1</sub>C. Later, plasma membrane specific antibody appears in the circulation and presumably saturates all free-binding sites on the deposited antigen which thereafter cannot be stained by immunofluorescent techniques. This fact might explain earlier failures to demonstrate the antigen in late biopsies. If this work can be reproduced by other investigators the initial impression of Schick in 1908 that PSGN represents serum sickness will be largely confirmed. Nevertheless, the reasons why some people develop the disease while others infected with nephritogenic streptococci do not, remains to be elucidated. Extrapolating from experimental models, one would expect that affected individuals would be good antibody producers against this lipoprotein antigen, while those with subclinical or no disease would have low or absent titers of antibody.

Another line of investigation which may yield additional understanding of PSGN as well as some other forms of glomerulonephritis is the study of cryoglobulins. These interesting macro-molecules have been found in a high percentage of patients with PSGN when specifically looked for with sensitive techniques. Most contain IgG plus B<sub>1</sub>C while IgM is also occasionally a part of the complex. These proteins can be shown to be biologically active in fixing complement and in causing glomerulonephritis when injected into animals. Nevertheless, the role in human disease at present remains unclear.

#### Membranous Glomerulonephritis

This common cause of the nephrotic syndrome in adulthood is characterized by the isolated finding of progressive, diffuse thickening of all glomerular basement membranes. Figure 10. The course is prolonged and variable with ultimate remission or death in uremia being equally common. At present there are few clues to the etiology. Immunofluorescent study repeatedly demonstrates granular deposition of IgG plus B<sub>1</sub>C along the thickened membranes, corresponding to electron dense subepithelial deposits (as in the Heyman model, Figure 8). That the disease is immune complex mediated is reasonably certain; however, the antigen involved, the reasons for the lack of cellular proliferation despite ongoing complex deposition, and the mechanism of remission are unknown. Since experimentally it is the clotting system which appears to initiate cellular proliferation, it may be that some characteristic of the complexes is different from that in other forms of immune complex disease or that the slow deposition and low levels of complexes are inadequate to trigger this mechanism. The protracted course over several years would suggest that the antigen involved is an endogenous, autologous one circulating in low concentration to which normal tolerance has been lost as in the Heyman model. However, remission under these circumstances is hard to understand. The recent finding of low levels of circulating cryoglobulins in most cases of membranous nephropathy may prove to be of great importance.

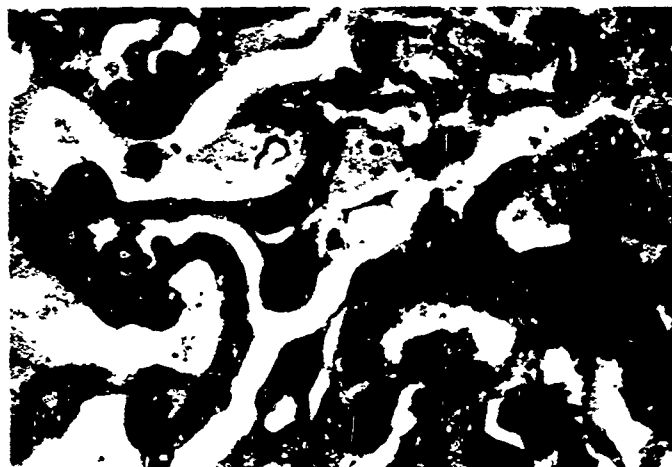


Fig. 10. Membranous glomerulonephritis showing severe thickening of all basement membranes.

#### Systemic Lupus Erythematosus Nephritis (SLE)

SLE represents one of the most intensively studied of the immune mediated diseases of humans. The repeated demonstration of antibodies to DNA, nucleoprotein, and other nuclear and cytoplasmic antigens in symptomatic patients has led to the conviction that these antibodies play a causative role in the peripheral manifestations of the disease. The recognition of renal disease as a major cause of morbidity and ultimate death in these patients has led to the widespread application of percutaneous renal biopsy for diagnostic and experimental evaluation of all stages of the illness. The growing body of evidence supports the conclusion that lupus nephritis is an immune complex disease expressing itself in at least three morphologic patterns with generally differing clinical severity and prognosis. The reasons for these differences are completely unknown but are probably related to differences in antibody, antigen, the quantity of circulating immune complexes, or in the presence and quantity of cryoglobulins.

The experimental observations implicating immune mechanisms in the development of lupus nephritis are many. Extensive study has shown anti-DNA antibodies to be specific for active lupus erythematosus. They are identified in the sera of most patients with active nephritis in varying titer generally corresponding to the severity of clinical manifestations.

That these antibodies are pathogenic has been suggested by their elution from affected renal tissue in much higher titer than in the corresponding serum. Furthermore, DNA antigen can be demonstrated in sera and glomeruli after antibody elution. Besides anti-DNA antibody and DNA antigen, antibodies against nucleoprotein and phosphate buffer-extractible nuclear antigens have also been found within affected glomeruli. Other antigen antibody systems may play an even more important role in the production of renal lesions. For instance, all patients having anti-ribosomal antibodies appear to manifest clinical renal disease. In addition, mixed cryoglobulins composed of IgG, IgM and perhaps other constituents are commonly seen in low titer in the sera of lupus patients and in some cases have been demonstrated as deposits within glomerular lesions. Finally, during periods of active renal disease, serum complement levels fall as in serum sickness and PSGN, suggesting the presence of biologically active circulating immune complexes.

By immuno-histochemical techniques and electron microscopy, complex deposition appears to have three distinct patterns corresponding to the different light microscopic morphologies. Cases with pure membranous changes have deposition of IgG, B<sub>1</sub>C in a finely granular pattern along the basement membranes. The only distinguishing feature from "idiopathic" membranous nephropathy lies in the slightly greater prominence of the mesangium in lupus. As expected, electron microscopy demonstrates subepithelial electron dense deposits corresponding to immune complex aggregates. Furthermore, the course and prognosis of this lesion generally parallels that of its idiopathic counterpart. In contrast to this pattern are the diffuse proliferative lesions usually leading to progressive deterioration and renal death. In these cases fibrinoid necrosis, wire loops, endothelial and mesangial cell swelling and proliferation are prominent features. Neutrophil infiltration and nuclear fragmentation appear in the more severely affected areas. Immunofluorescent studies show localization of IgG and B<sub>1</sub>C in coarse lumps along the basement membrane and in mesangial cells. Fibrinogen derivatives can be seen in the same pattern. By electron microscopy large dense deposits are located subendothelially, often partially or completely phagocytized by endothelial and mesangial cells. Figure 11. Other deposits can be found within the capillary lumens either free or within polymorphonuclear cells. Occasional deposits are also seen lying within

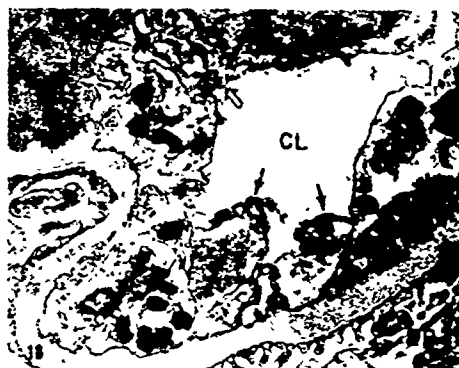


Fig. 11. Electron micrograph of a glomerular capillary loop from a patient with diffuse lupus nephritis. EN = endothelial cell nucleus, CL = capillary lumen, EP = epithelial cell with foot processes lying on basement membrane. Note the dense deposit marked by asterisk as well as the deposits shown by arrows covered by endothelial cell cytoplasm.

the basement membrane or on the subepithelial side. This distribution of immunoglobulins, complement, and fibrin has been described occasionally in severe cases of PSGN as well as in idiopathic membranoproliferative glomerulonephritis. The mechanism behind this mesangial and subendothelial deposition in contrast to the membranous pattern is not understood but may relate to the composition, size, or quantity of these macro-molecules in the circulation. Experimental evidence in animals and the presence of fibrin and fibrinogen derivatives in human lesions implicate the coagulation system as causing at least part of the observed tissue injury. It can easily be imagined that subendothelial deposits in contact with the circulation would be more biologically active than subepithelial ones. Nevertheless, proof of the pathogenicity of these deposits thus far is incomplete, and the exact details linking these immune complexes to the subsequent nephritis are unknown.

The third pattern of SLE renal involvement is focal and local proliferation with occasional necrosis of glomerular tufts. This form is usually associated with good prognosis and rapid response to corticosteroids. Occasionally, progression to more generalized proliferative disease is seen, however. Immunofluorescent studies indicate mild diffuse deposition of IgG and B<sub>1</sub>C along basement membranes with heavier deposition within lesions and mesangial areas. To answer whether or not the differences between this pattern and the

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diffuse proliferative type are qualitative or merely quantitative will require much additional study.

*Lipoid Nephrosis (Nil disease, minimal change disease)*

This lesion is present in most cases of childhood nephrotic syndrome and is seen in about 25 percent of adults presenting with nephrosis. The histology by light microscopy consists of either no change from normal or occasional focal, local thickening of basement membranes. In long standing recurrent cases, focal areas of scarring, irregular mild basement membrane thickening, increase in mesangial cells and matrix and obsolescent glomeruli are found. Immunofluorescent studies looking for deposition of IgG, IgM, and B<sub>1</sub>C have been uniformly unsuccessful. Under electron microscopy there is fusion of epithelial cell foot processes, believed to represent a nonspecific normal reaction to increased protein passage across the basement membrane barrier. Occasional small subendothelial dense deposits have been reported but apparently bear no relationship to areas of basement membrane thickening. More common are areas of platelet aggregation and occasional fibrin thrombi within capillary lumina. These findings may explain the gradual scarring and glomerular obliteration seen in long standing cases.

Although it was formerly believed that lipoid nephrosis merely represented an early stage of idiopathic membranous nephropathy, it is now clear that these are two distinct diseases unrelated to each other. No convincing cases of progression from the one to the other have ever been presented, the distinctly different ultrastructural morphologies clearly explain why.

The repeated failure to demonstrate immunoglobulin deposition has suggested to some workers a possible metabolic or biochemical cause unrelated to immune mechanisms. Nevertheless, the high incidence of atopy and eosinophilia in many cases, as well as the sensitivity of the lesion to corticosteroid therapy, has convinced many investigators that significant immune events were being somehow missed by routine procedures. Consequently, the recent report by Gerber and Paronetto may represent a significant breakthrough in the understanding of this disease. By preparing antibody in goats through the use of rare IgE myeloma protein, they have been able to demonstrate linear deposition of IgE in a comma like

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fashion along basement membranes in all cases of lipoid nephrosis studied. Unfortunately, other glomerular diseases studied also showed this reaction, suggesting that it may be a non-specific finding. Although much further work will be necessary to clarify the pathogenic role, if any, played by this immunoglobulin deposition, at least one line of investigation is now available.

*Membranoproliferative Glomerulonephritis*

This group is a mixed bag of morphologic lesions and clinical expressions. Under this heading will be included such entities as diffuse proliferative glomerulonephritis associated with nephrotic syndrome, chronic hypocomplementemic nephritis of childhood, lobular glomerulonephritis, necrotizing glomerulonephritis, some patients with acute post streptococcal glomerulonephritis pursuing a rapidly progressive course, as well as cases having similar histology but no antecedent streptococcal exposure. An immune basis for these diseases seems likely, but few cases have been well-studied from that point of view. Most cases have normal complement levels except for those patients with hypocomplementemic nephritis in which selective degradation of  $C_3$  by an unidentified serum factor occurs. Electron microscopy shows subendothelial and mesangial deposits similar to the proliferative form of lupus nephritis. Immunofluorescent staining of IgG and B $_2$ C in a lumpy pattern is commonly, but not consistently, seen. Prognosis is generally poor except when a streptococcal etiology is present. Since some of these cases may present with rapid clinical deterioration associated with epithelial proliferation and crescent formation indistinguishable from RPGN, the examination of these biopsies with electron microscopy and immunofluorescence is mandatory. Again the findings of fibrinoid necrosis and fibrin thrombi suggest an intimate role for the coagulation process especially in the more severe cases. It is likely that the renal involvement of Henoch-Schoenlein purpura, hypersensitivity angitis, and Wegener's granulomatosis is similar in mechanism to these membranoproliferative diseases.

*Immune Complex Nephritis with Known Antigens*

Under this heading may be included the nephrotic syndrome of penicillamine therapy, persisting Australia antigenemia, secondary syphilis, and at least one case of carcinoma. In

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addition the acute glomerulonephritis of falciparum malaria is most likely related to immune complex deposition. In the cases of disease related to Australian antigen and quartan malaria, antigen has been definitely shown to be deposited within affected glomeruli along with IgG and B<sub>1</sub>C. When IgG was eluted from a patient with membranous glomerulonephritis and carcinoma of the lung, antibody specific for tumor antigens was found. Unfortunately, efforts were not made to identify tumor antigen within the glomerular immune deposits. Thus far, efforts to demonstrate penicillamine in immune deposits has been unsuccessful, probably for reasons of technique. In cases of secondary syphilis with nephrosis no efforts have been made to demonstrate the causative antigen, although lumpy deposits of IgG have been identified by electron microscopy and immunofluorescence. No doubt the presence of treponema antigen will be demonstrable in these deposits when properly studied.

*Suggested Reading*

- Bacani RA, Valeasquez F, Kanter A, et al: Rapidly progressive (non streptococcal) glomerulonephritis. Ann Intern Med 69:463-485, 1968
- Baldwin DS, Lowenstein J, Rothfield NF, et al: Clinical course of the proliferative and membranous forms of lupus nephritis. Ann Intern Med 73:929-942, 1970
- Barratt TM, Soothill JF: Controlled trial of cyclophosphamide in steroid-sensitive relapsing nephrotic syndrome of childhood. Lancet 2:477-482, 1970
- Benoit FL, Rulon DB, Theil GB, et al: Goodpasture's syndrome. A clinicopathologic entity. Amer J Med 37:424-444, 1964
- Cameron JS, Glasgow EF, Ogg CS, et al: Membranoproliferative glomerulonephritis and persistent hypocomplementemia. Brit Med J 4:7-14 (3 Oct), 1970
- Carpenter CB: Immunologic aspects of renal disease. Ann Rev Med 21:1-16, 1970
- Christian CL: Immune complex disease. New Eng J Med 280:878-884, 1969
- Comerford FB, Cohen AS: The nephropathy of systemic lupus erythematosus. Medicine 46:425-473, 1967

*Immunology of Glomerulonephritis* Stemmler

- Dixon FJ: The pathogenesis of glomerulonephritis. Amer J Med 44:493-498, 1968
- Gerber MA, Paronetto F: IgE in glomeruli of patients with nephrotic syndrome. Lancet 1:1097-1099 (May 28), 1971
- Good RA, Finstad J, Cain WA, et al: Models of immunologic diseases and disorders. Fed Proc 28:191-205, 1969
- Heptinstall RH: Pathology of the Kidney. Boston: Little, Brown and Company, 1966, pp 235-396
- Herdmann RC, Edson JR, Pickering RJ, et al: Anticoagulants in renal disease in children. Amer J Dis Child 119:27-35, 1970
- Kincaid-Smith P, Laver MC, Fairley KF: Dipyridamole and anticoagulants in renal disease due to glomerular and vascular lesions. Med J Australia 1:145-151 (24 Jan), 1970
- Koffler D, Kunkel HG: Mechanisms of renal injury in systemic lupus erythematosus. Amer J Med 45:165-168, 1968
- Lange K, Tresar G, Sagel I, et al: Routine immunohistology in renal diseases. Ann Intern Med 64:25-40, 1966
- Lewis EJ, Covallo T, Harrington JT, et al: An immunopathologic study of rapidly progressive glomerulonephritis in the adult. Human Pathology 2:185-208, 1971
- McCluskey RT: Evidence for immunologic mechanisms in several forms of human glomerular diseases. Bull NY Acad Med 46:769-788, 1970
- Michael AF, Drummond KN, Good RA, et al: Acute post streptococcal glomerulonephritis: Immune deposit disease. J Clin Invest 43:237-248, 1966
- Rosen S: Membranous glomerulonephritis. Current status. Human Pathology 2:209-231, 1971
- Schreiner GE: The nephrotic syndrome. In Diseases of the Kidney. Strauss MB, Welt LG (eds). Boston: Little, Brown and Company, 1965, p 335
- Schur PH, Austen KF: Complement in human disease. Ann Rev Med 19:1-24, 1968
- Schur PH, Sandson J: Immunologic factors and clinical activity in systemic lupus erythematosus. New Eng J Med 278:533-538, 1968
- Segal BC, Andres GA, Hsu KC, et al: Studies on the pathogenesis of acute and progressive glomerulonephritis in man by immunofluorescein and immunoferritin techniques. Fed Proc 24:100-108, 1965
- Strauss MB: Immunosuppressive treatment of proliferative glomerulonephritis. New Eng J Med 285:632-633, 1971
- Tresar G, Sewar M, Ty A, et al: Partial characterization of antigen c streptococcal plasma membrane components in acute glomerulonephritis. J Clin Invest 49:762-768, 1970

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Vassalli P, McCluskey RT: The coagulation process and glomerular disease. Amer J Med 39:179-183, 1965  
White RHR, Glasgow EF, Mills RJ: Clinicopathological study of nephrotic syndrome in childhood. Lancet 1:1353-1359, 1970

## THE MALIGNANT PHASE OF HYPERTENSION

Relationship of the Kidney with Pathogenesis, Prognosis, and Therapy

Allan B. Schwartz, M.D.\*

Malignant hypertension is a devastating entity. It is not a distinct disease itself but should be considered a syndrome representing a specific phase of hypertension having various etiologic possibilities. The etiologies vary from primary essential hypertension with nephroangiosclerosis to nephritis, lupus nephritis, et cetera. The one common feature that the long list of etiologic considerations have is renal involvement. By definition, the malignant phase of hypertension must have an abnormality in some parameter of renal evaluation or the diagnosis is tenuous. Schottstaedt and Sokolow /1/ in their 1953 review of clinical parameters associated with the malignant phase of hypertension found high percentages of cerebral and cardiac involvement but found 100 percent renal involvement in their study of 104 cases. They wrote, "The kidney is the organ most seriously involved in malignant hypertension". Renal involvement is recognized by proteinuria on urinalysis and abnormal renal functional parameters such as azotemia or elevated serum creatinine. These crude parameters call attention to the obvious loss of renal function threatening to result in uremia and that should the malignant phase of hypertension go unchecked. The malignant phase of hypertension is a vascular disease for certain. Histologically, fibrinoid necrosis of arterioles throughout the body has been recognized as the classic lesion.

As to the pathophysiology of the malignant phase of hypertension, no clear explanation is yet available. It appears that some primary alteration occurs in arteriolar structural integrity, reducing luminal area and the effective perfusion volume of the arteriole, i.e. reducing the available vascular space. And, as stated by Poiseuille's law (resistance to viscous flow varies inversely with the fourth power of the radius), this reduction in vascular radius dramatically increases peripheral vascular resistance. Cardiac systolic ejection force attempts to compensate for this increased vascular resistance by producing a more forceful ejection and a

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progressive increase in systolic pressure becomes apparent. At these excessive pressures, further alterations of stretching and constriction of arterioles results and a vicious cycle is set in motion. As a result, there is a progressive increase in both diastolic and systolic pressure.

Further vascular alterations occur as plasma appears locally in zones of dilatation in the walls of terminal arterioles at an early stage in the process. Local over stretching or tearing of medial muscle fibers occurs which may simultaneously destroy the muscle and turn the vessel into a semi-permeable membrane. This allows various colloid materials to escape into the tissue while the destroyed vascular tissue itself becomes saturated with concentrated plasma proteins giving the appearance of fibrin, i.e. fibrinoid necrosis. /2/

Recently, evidence has arisen that points to a hematology coagulation abnormality associated with the vascular changes of malignant hypertension. An increase in permeability of small blood vessels has been thought to set in motion the fibrin deposition in the wall and in the lumen of vessels. These fibrin deposits then induce fragmentation of red blood cells, which leads to microangiopathic hemolytic anemia which then results in further deposition of fibrin until finally the vessel is occluded and the peripheral vascular resistance is maximum. /3/

Another area of research has to do with a deposition of lipid-like material in subendothelial areas of glomerular capillaries. These lipid deposits have been demonstrated by electron microscopic examination of glomerular capillaries from renal biopsies of patients having the malignant phase of hypertension. /4/

The humoral and neurogenic aspects of the malignant phase of hypertension are still open to question. Peart /5/ suggested that aldosterone excess was a defense mechanism brought out to counteract the angiotensin induced sodium loss. Oversecretion of aldosterone in malignant hypertension was believed by Cope and Pearson /6/ to be a consequence of renal damage. Laragh, Sealey, and Sommers /7/ in 1966, found a strong correlation between secondary hyperaldosteronism of malignant hypertension and increased levels of plasma renin. These data strongly suggested a renal course of stimulation

for the hyperaldosteronism observed in the more advanced stages of the malignant phase of hypertension. Certainly, some of the highest plasma renin activity values that have been recorded have been in malignant hypertension.

Intravenous injection of angiotensin has been implicated in causing fibrinoid necrosis in the rat as has a partly purified renin preparation. /8,9/ This ability to produce necrotic vascular lesions is also shared by various pressor amines such as tyramine, ~~methoxamine~~, and norepinephrine. /10-12/

Amine hypertension has been recognized clinically. Foods such as cheeses and fermented material such as beer contain tyramine which has been shown to elevate blood pressure by releasing norepinephrine. /13/ In the presence of monoamine oxidase inhibition, the usual degradation of norepinephrine is retarded and excessive tyramine ingestion may provoke severe or even malignant hypertension. Certainly, pheochromocytoma has been a recognized cause of malignant hypertension.

The relationship between the sympathetic nervous system, catecholamines, and renal humoral mechanisms have been well established. Wathen et al /14/ in 1958, demonstrated the relationship between catecholamines and the renin-angiotensin system by infusing norepinephrine in anesthetized dogs and evoking an acute release of renin. Michelakis and Horton /15/ in 1970, confirmed this relationship in man by infusing norepinephrine in human volunteers and evoked an increase in peripheral plasma renin activity. It is possible that this interrelationship between the sympathetic nervous system and the renin-angiotensin system could be intimately involved as the "trigger mechanism" of the malignant phase of hypertension.

It is also possible that an existing renal parenchymal disease could in itself intrinsically initiate an abnormal humoral vasopressor substance which alone could be the "trigger mechanism" of the malignant phase of hypertension. There is already evidence for a renal humoral vasopressor substance existing as a major factor responsible for the blood pressure elevation and vascular damage of the malignant phase of hypertension. /16/ This vasopressor effect of the kidney has been presented in the setting of both primary essential hypertension and chronic renal parenchymal disease, i.e. chronic glomerulonephritis.

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I am certain it is obvious to the reader that I am fostering the concept that there is a peripheral vascular alteration that initiates the malignant phase of hypertension. The question that arises is, "What triggers the vascular alteration?". It is interesting to hypothesize that this "trigger mechanism" might involve a renal-sympathetic nervous system catecholamine mechanism which once set in motion will develop into a vicious cycle resulting in arteriolar fibrinoid necrosis.

The clinical syndrome of the malignant phase of hypertension is a reflection of the diffuse vascular alterations, specifically fibrinoid necrosis and the resultant compromised perfusion of vital organs - brain, heart, kidneys and eyes.

That the above process is reversible is a thesis gaining support each year. The blood pressure must be reduced to allow vascular changes to heal. The resistance vessels may return to their normal caliber, perfusion will improve, and the syndrome will abate.

#### PROGNOSIS OF MALIGNANT HYPERTENSION

The prognosis of malignant hypertension is definitely improved today over 20 years ago and even 10 years ago. The apparent reasons for this improvement are twofold: (1) the availability of relatively safe, potent antihypertensive agents which have been developed for clinical use during the period, and (2) an increasing knowledge and understanding of the use of the antihypertensive agents in the presence of renal insufficiency associated with the malignant phase of hypertension.

Before the advent of such early therapy as sympathectomy, malignant hypertension was consistently a fatal disease in a maximum of four or five years and 80 percent fatal in the first year. /17-19/ In 1938, Page /20/ reported on beneficial results of anterior nerve root section. He was the first to show an improvement in the course of malignant hypertension in that there was some evidence of improvement of cardiac parameters, eye grounds, and renal function. The patient still eventually succumbed to the disease, however.

The advent of ganglionic blocking agents and adrenergic blocking agents brought about an improvement in the survival statistics. Encephalopathic and cardiac causes of death associated with malignant hypertension declined. However, the percentage of renal causes of death increased demonstrating a failure to arrest the arteriolar fibrinoid necrosis within the kidney.

In 1956, McCormack et al /21/ showed definite evidence of healing of acute destructive lesions of malignant nephroangiosclerosis in patients treated with potent antihypertensive agents including hexamethonium, pentolinium, chlorosondamine, mecamylamine, reserpine, and hydralazine. Although an autopsy study, there had been some transient clinical remissions effected in these patients with malignant nephroangiosclerosis by intensive treatment with the agents noted above. Renal failure was the primary cause of death of 14 out of 19 treated patients. There was a definite "cessation of activity and a regression in both arteriolar necrosis and thrombonecrosis". This was associated with disappearance of most of the foci of fibrin accumulation and of the evidence of acute vascular damage.

McCormack et al /21/ noted in their review that in some cases treatment was not wholly effective and minimal active lesions of malignant nephroangiosclerosis persisted and were apparently progressive, although certainly not nearly as rapidly as in the untreated patient. Their words were not heeded and, for the next few years, hypertensiologists feared treatment of malignant hypertension associated with renal insufficiency.

The relationship of renal insufficiency and survival rate of patients with malignant hypertension has been interesting to follow through the evolution of successful anti-hypertensive therapy.

In 1959, Harington et al /22/ reported that malignant hypertension associated with a blood urea nitrogen of greater than 60 mg/100 cc before therapy correlated with only a 10 percent survival by two years. Those patients with a blood urea nitrogen less than 60 mg/100 cc had a 55 percent survival by two years.

In 1961, Dollery /23/ expressed the opinion that progressive renal failure could not be halted by antihypertensive therapy. With respect to the blood urea level, he reported only a 15 percent one year survival if malignant hypertension was accompanied by a blood urea level of over 60 mg/100 cc (blood urea nitrogen greater than 30 mg/100 cc). The one year survival for patients having malignant hypertension and a blood urea level less than 60 mg/100 cc was 73 percent.

In a report by Mohler and Freis /24/ in 1960, a correlation of five-year survival was made with normal or nearly normal levels of nonprotein nitrogen before treatment.

Sokolow and Perloff /25/ reported a five-year survival of 5 of 11 patients who had creatinine clearance values greater than 45 cc/min before therapy with ganglionic blocking agents. Of 15 patients with poor renal function before treatment, none survived even three years.

Kirkendall /26/ wrote that successful lowering of blood pressure improved signs of necrotizing arteriolitis that allowed histologic improvement. To produce the same improvement of histology in the kidney "one must reduce the blood pressure and blood flow to the kidneys so that glomerular filtration rate and renal excretory function are reversibly decreased." Thus, one is on the horns of a dilemma! /26/ Kirkendall in 1961, as were many others, was faced with the fact that the closer to normotension the patient came, the worse the renal function became during the early phase of treatment of the malignant hypertension. The key to the above quotation is that aggressive reduction of blood pressure might initially lower renal function, but this initial decline is a functional one that is "reversible".

Through the 1960's, physicians were still unable to cope with malignant hypertension coexisting with significant renal insufficiency. Therapy was often withheld or ineffectively administered at the first hint of blood urea nitrogen rise. As recently as 1966, Langford and Bonas /27/ advocated that when a rise in blood urea nitrogen occurs, it is usually best to hold the pressure at the level that has been obtained or even to let the blood pressure go slightly higher rather than immediately pressing on to further blood pressure reduction. They did, however, recognize the need to continue antihypertensive therapy in treating malignant hypertension despite the

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rise in blood urea nitrogen to permit healing of the necrotizing arteriolitis. They also agreed that it may be necessary to utilize dialysis while hypotensive therapy was being given in the face of worsening renal function.

Schroeder /28/ claimed that if improvement in renal function does not occur early, the treatment can be considered only life extending and he predicted a steadily progressive mortality. He did, however, recognize the value of effective lowering of blood pressure of malignant hypertension with mild to moderate renal insufficiency and noted that in his experience, one-quarter of such treated patients survive five years.

Woods and Blythe /29/ appear to have the most encouraging experience in the literature dealing with survival of patients having malignant phase of hypertension complicated by severe renal insufficiency. These authors of aggressive therapy treated 20 patients with malignant hypertension and a blood urea nitrogen of 50 mg/100 cc or higher and noted a 55 percent one-year survival, and a 35 percent two-year survival and a 25 percent longer term survival.

In 1969, it was again reported that aggressive treatment of accelerated hypertension in patients with azotemia resulted in slight worsening of renal function during the first two weeks. However, by three months of effective treatment, renal function had improved to levels better than pretreatment values. /30/

The conclusion is that reduction of blood pressure to normal levels in patients with malignant phase of hypertension complicated by renal insufficiency does not necessarily result in irreversible deterioration of renal function and may actually improve renal function in a large proportion of patients.

At Hahnnemann it is obvious to our staff that the only way to attack malignant hypertension associated with primary nephroangiosclerosis is to lower promptly and aggressively the blood pressure to normotensive levels. However, primary renal parenchymal disease, such as chronic glomerulonephritis and lupus nephritis, may be associated with a secondary form of malignant hypertension which presents entirely different

considerations. The physician is now faced with the necessity of considering two separate prognostic aspects in one patient, i.e. "What is the prognosis of the primary renal parenchymal disease and what is the prognosis of the secondary and co-existing malignant hypertension?". Renal insufficiency might be a definite feature of either. The clear distinction must be made early between malignant hypertension due to primary nephroangiosclerosis versus malignant hypertension due to primary renal parenchymal disease. Often, the only means by which the distinction can be made is the kidney biopsy. Once the diagnosis of primary nephroangiosclerosis is established, the treatment program for the malignant phase of hypertension with renal insufficiency is clear cut — normotension must be acquired and maintained.

Normotension provides the only setting in which the necrotizing arteriolar changes within the kidney will heal. Normotension must be maintained even if renal insufficiency appears to worsen in the early phase of treatment. This further loss of glomerular filtration rate manifesting a rise in serum creatinine and blood urea nitrogen is a functional, reversible loss.

The sudden decrease in perfusion pressure resulting from the antihypertensive prescription will result in a decreased glomerular filtration rate. A transient worsening of azotemia and even uremia may occur during the early vascular healing phase. A need for supportive peritoneal dialysis or hemodialysis therapy may become apparent in some cases. Certainly, if the diagnosis is made early and treatment initiated early, this need will be transient. Once the fibrinoid vascular changes have healed and renal arterioles are again patent, the glomerular perfusion will improve and glomerular filtration rate will gradually increase. Such an example is represented in the following case presentation.

#### CASE REPORT

The patient is a 32-year-old black female who presented with a one-week history of rapidly progressing dizziness, severe suboccipital headache, and nausea. On the day of admission, she had several episodes of vomiting. There was no

*Malignant Phase of Hypertension - Schwartz*

past history of renal disease, hypertension, cardiovascular disease, or diabetes. The family history was negative for hypertension.

The physical examination demonstrated the blood pressure to be 230/156 mm Hg in the right arm and 228/152 mm Hg in the left arm. Pulse rate was 96 beats/min and regular. Oral temperature was 98.6 F. Funduscopic examination revealed severe arteriolar spasm, soft cottonwool exudates, flame shape hemorrhages, and papilledema bilaterally. The heart examination demonstrated the point of maximal impulse in the sixth intercostal space in the anterior axillary line. A prominent left ventricular heave was noted. An atrial gallop was present. A grade III/VI early systolic ejection murmur was noted at the second right intercostal space. The lung fields were clear. Abdominal examination showed no palpable liver, spleen, or kidneys. There was no costovertebral angle tenderness and there was no abdominal bruit. Femoral pulses were strong bilaterally. All peripheral pulses were found to be normal. There was a trace of pretibial and pedal edema bilaterally. The neurologic evaluation showed the patient to be moderately lethargic, but she was well-oriented for time, place, and person. There was no nuchal rigidity and no localizing neurologic abnormality.

Laboratory evaluation demonstrated the blood urea nitrogen to be 109 mg/100 cc, serum creatinine 11.5 mg/100 cc, serum sodium 137 mEq/L, serum potassium 3.8 mEq/L, serum chloride 98 mEq/L, and serum carbon dioxide combining power 20.9 mEq/L. Urinalysis demonstrated 8-10 red blood cells/HPF and 10-15 white blood cells/HPF, and a one plus reaction to protein. Tests for urine, sugar, and acetone were negative. Urine specific gravity was 1.005. Complete blood count showed a hematocrit of 29 percent, hemoglobin of 9.6 gm/100 cc, white blood count of 5,150 with 65 percent segmented forms, 5 percent bands, and 30 percent lymphocytes. The peripheral plasma renin activity was 5000 ng/100 cc (Method of Boucher). The initial therapy consisted of alpha-methyldopa 500 mg intravenously and furosimide 80 mg intravenously. The alpha-methyldopa was repeated in a dose of 500 mg intravenously every six hours for four doses. At that time, the patient was started on oral therapy consisting of alpha-methyldopa 500 mg every six hours in combination with hydralazine 50 mg every six hours and furosimide 80 mg every 12 hours. Within 12 hours after the patient's admission, the blood pressure was reduced to 120/80 mm Hg and within 24 hours the oral medication described above was maintaining a blood pressure of 100/70 mm Hg in the supine position.

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Three days later the blood urea nitrogen had increased to 150 mg/100 cc and the serum creatinine had risen to 16.2 mg/100 cc. A renal arteriogram demonstrated patent main renal arteries bilaterally. There was moderate arcuate and interlobular arterial narrowing within the renal cortex. The transit time of the radiopaque material was delayed and there was absence of nephrogram effect. On the fifth hospital day the blood urea nitrogen was noted to have increased to 193 mg/100 cc and the serum creatinine was 15.3 mg/100 cc. The patient had developed further evidence of uremia and peritoneal dialysis was instituted for the ensuing 48-hour period. Open renal biopsy was then performed. The renal biopsy demonstrated evidence of fibrinoid necrosis of the afferent arterioles and interlobular arterioles. Figure 1. There was also typical onion-skin effect in arterioles diffusely throughout the kidney. Figure 2. The interstitium was moderately involved with round cell inflammatory reaction, edema, and a mild degree of fibrosis. The glomeruli were nonspecifically thickened and minimally proliferative. Figure 3. Only a few of the glomeruli were entirely hyalinized. Two 24-hour urines for vanillylmandelic acid excretion, were 6 mg/24 hours and 7 mg/24 hours. Repeated urinary cultures demonstrated no significant growth.

The clinical course was marked by normotensive response to the medications (furosimide, hydralazine, and alpha-methyl dopa). The patient showed continuous improvement in overall well-being. Over the next three weeks, there was a stabilization of the blood urea nitrogen at 14 mg/100 cc and the serum creatinine at 11.3 mg/100 cc.

An orthostatic response to the medications was noted as the blood pressure was consistently lower in the standing posture than it was in the supine posture. The average blood pressure in the standing posture was 115/80 mm Hg and the average blood pressure in the supine posture was 170/100 mm Hg during the patient's hospitalization. For this reason, the patient's bed was tilted 30 degrees upright at the head. The patient was discharged and followed at frequent intervals as an outpatient. Medications were continued and occasional adjustments were made to maintain normotensive blood pressure levels. Associated with the marked orthostatic response noted, three episodes of dizziness occurred during the next few months. However, there was no syncope. Again the supine blood pressure was consistently higher than the normotensive-to-slightly-hypotensive standing blood pressure. The patient's bed at home

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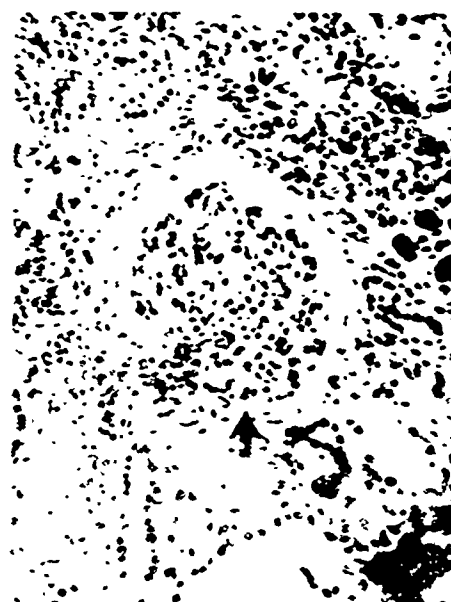
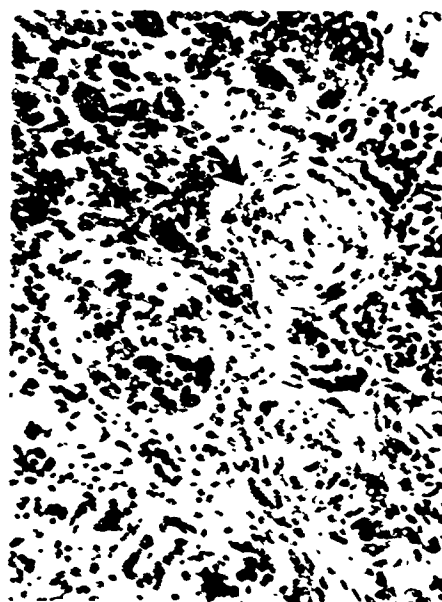
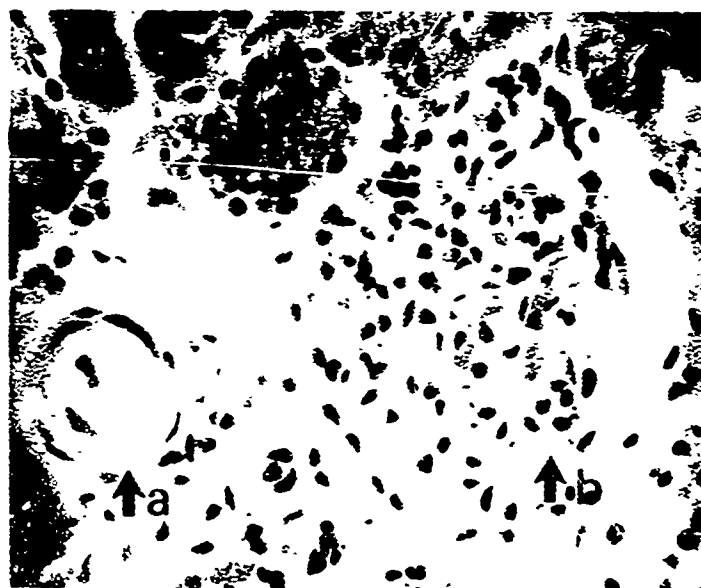


Fig. 1. (*top*) Renal biopsy during acute phase (H&E, x360). Arrow a indicates fibrinoid necrosis of arteriole, and arrow b indicates nonspecific thickening and proliferation of glomerulus.

Fig. 2. (*lower left*) Obliteration of interlobular artery by "onion skin" effect (H&E, x180).

Fig. 3. (*lower right*) Mild nonspecific thickening and proliferation of glomerulus (H&E, x180).

was placed in the 30 degree head-up tilt position to avoid the mild blood pressure elevations while she slept.

During the outpatient follow-up period, the patient was trained to record her own blood pressures at home. She kept an extremely accurate record which corresponded well with the in-office readings.

The funduscopic picture cleared over the initial three months of outpatient follow-up and her residual funduscopic changes consisted of mild arteriolar narrowing with no evidence of hemorrhages or exudates.

The patient returned to work after three months and maintained full employment following that date.

The blood urea nitrogen and serum creatinine progressively decreased over the next few months, and within two months the creatinine clearance increased to 30 ml/min.

After having maintained a steady improvement while normotensive for seven months, the patient was readmitted to the hospital for elective evaluation of her renal status. The repeated kidney biopsy showed definite evidence of afferent and interlobular arteriolar patency. Figure 4. There was no evidence of the typical onion-skin effect and fibrinoid necrosis which had been noted in the initial biopsy. Many glomeruli did show some evidence of shrinking and there was an increase of Bowman's space. Figure 5. However, the glomerular capillaries were no longer thickened and the degree of proliferation was less than had been noted in the initial biopsy. The creatinine clearance was 30 ml/min and the serum creatinine was 3.6 mg/100 cc.

Repeated evaluation of the peripheral plasma renin activity demonstrated values below 1000 ng/100 cc in contrast to the initial value of 5000 ng/100 cc during the initial hospitalization.

The patient was then seen at monthly intervals. She maintained a normotensive blood pressure in the upright posture and a minimum degree of hypertension was recorded only occasionally in the supine posture. The medication was continued rigidly by the patient. Thirteen months after initial treatment the patient's blood urea nitrogen was 42 mg/100 cc and

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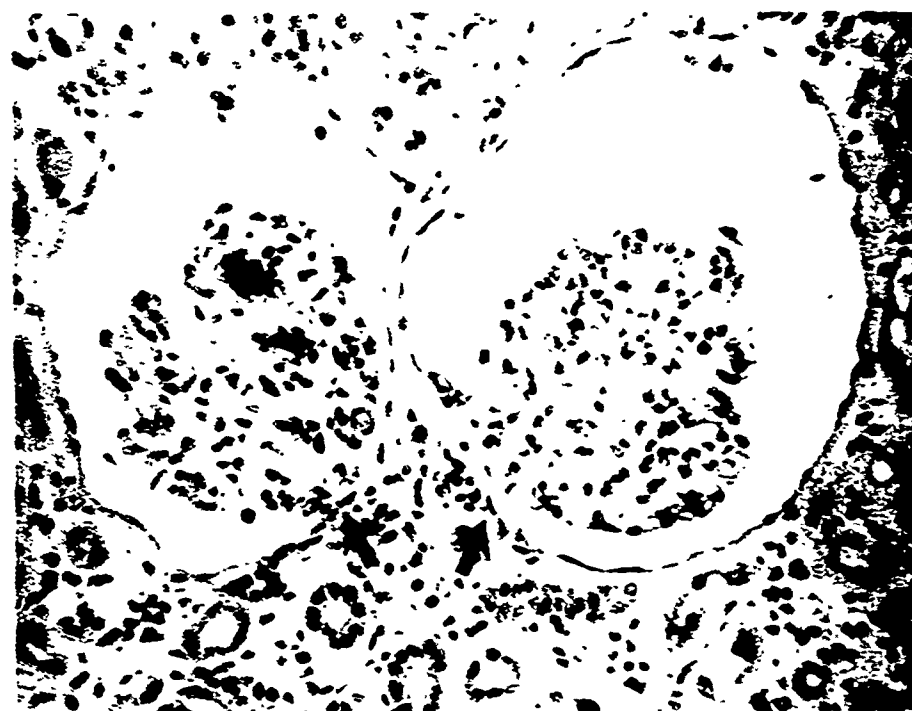
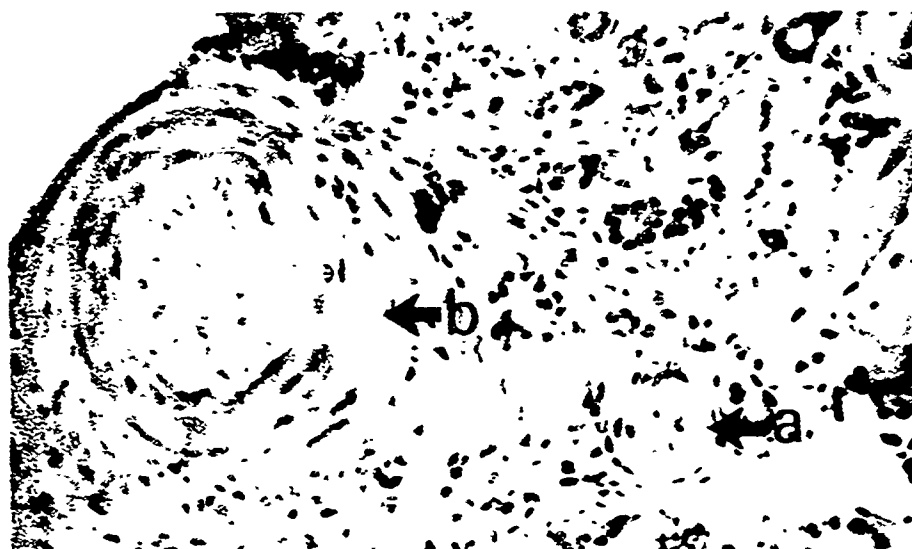


Fig. 4 (top). Renal biopsy after seven months of treatment. Arrow 'a' indicates afferent arteriole patency and arrow 'b' indicates interlobular arteriole patency. Both are still present (H&E, X360).

Fig. 5 (bottom). Renal biopsy after seven months of treatment. Glomerular capillary loops are more delicate, however, size of glomeruli is mildly shrunk and in this case Bowman's space is present (H&E, X360).

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serum creatinine was 2.9 mg/100 cc, and the creatinine clearance was 35 ml/min. Figure 6. The patient has maintained full employment in the capacity of laboratory technician. The antihypertensive prescription at present is: furosimide 80 mg twice daily, hydralazine 100 mg four times daily, alpha methyl dopa 500 mg four times daily.

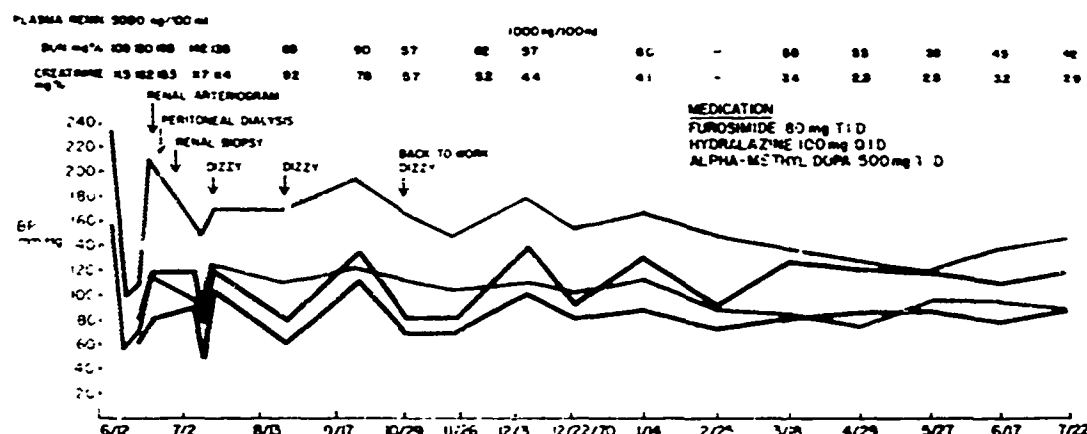


Fig. 6. Summary of patient's clinical course and treatment.

*References*

- Schottstaedt MF, Sokolow M: The natural history and course of hypertension with papilledema (malignant hypertension). *Amer Heart J* 45:331-362, 1953.
- Byron FB: *The Hypertensive Vascular Crisis*. New York: Grune and Stratton, Inc., 1969.
- Linton AL: Microangiopathic hemolytic anemia and the pathogenesis of malignant hypertension. *Lancet* 1:1277-1282, 1969.
- Veress B, Jelliner H, Kocze A, Venesz I: The distribution of lipids in malignant hypertensive fibrinoid necrosis. *J Atheroscler Res* 10:55-61, 1969.

5. Peart WS: Possible relationship between salt and the angiotensin system in essential hypertension. (In book unknown) by KD Bock and PT Cottier (eds). Berlin: Springer-Verlag, 1960.
6. Cope CL, Pearson J: Aldosterone secretion in severe renal hypertension. Clin Sci 25:331-341, 1963.
7. Laragh JH, Sealey JE, Sommers SE: Patterns of adrenal secretion and urinary excretion of aldosterone and plasma renin activity in normal and hypertensive subjects. Circ Res 18:158-174, 1966.
8. Byron FB: Angiotensin and renal vascular damage. Brit J Exp Path 45:7-12, 1964.
9. Asscher AW, Anson SG: A vascular permeability factor of renal origin. Nature 198:1097-1099, 1963.
10. Duff GL, Hamilton JD, Magner D: Experimental production of arteriolonecrosis and medionecrosis of arteries by means of tyramine injection. Proc Soc Exp Biol Med 41:295-1939.
11. Herbertson BM, Kellaway JD: Arterial necrosis in the rat produced by methoxamine. J Path Bact 80:87-92, 1960.
12. Giese J: Acute hypertensive vascular disease. II Studies on vascular reaction patterns and permeability changes by means of vital microscopy and colloidal tracer technique. Acta Path Microbiol Scand 62:497-515, 1964.
13. Comroe JH Jr: The mechanism of action of some drugs on the sympathetic nervous system. Physiol Physicians 1:5-8, 1963.
14. Wathen RL, Kingsbury WS, Stouder DA, et al: Effects of infusion of catecholamines and angiotensin II on renin release in anesthetized dogs. Amer J Physiol 209:1012-1024, 1965.
15. Michelakis AM, Horton R: The relationship between plasma renin and aldosterone in normal man. Circ Res 26 and 27 (suppl):185-194, 1970.
16. Onesti G, Schwartz A, Swartz C, Ramirez O, Brest AN: Vascular factors in renal hypertension. (Abstract) Circulation 37 and 38 (suppl):150, 1968.
17. Bjork S, Sannerstedt R, Angervall G, et al: Treatment and prognosis in malignant hypertension. Clinical follow-up study of 93 patients on modern medical treatment. Acta Med Scand 166:175-187, 1960.
18. Keith NM, Wagener HP, Barker NW: Some different types of essential hypertension: Their course and prognosis. Amer J Med Sci 197:332-343, 1939.

## Malignant Phase of Hypertension Schwartz

19. Kincaid-Smith P, McMichael J, Murphy EA: The clinical course and pathology of hypertension with papilledema (malignant hypertension). Quart J Med (New Series) 27:117-153, 1958.
20. Page IH: Medical aspects of surgical treatment of hypertension. JAMA 110:1161-1165, 1938.
21. McCormack LJ, Beland JE, Schneekloth RE, et al: Effect of antihypertensive treatment on the evaluation of the renal lesions in malignant nephrosclerosis. Amer J Path 34:1011-1021, 1958.
22. Harrington M, Kincaid-Smith P, McMichael J: Results of treatment in malignant hypertension. A seven year experience in 94 cases. Brit Med J (No. 5158) 2:969-980, 1959.
23. Dollery CT: Malignant hypertension. In Treatment of Hypertension. Pickering GW, Cranston WI, Pears MA (eds). Springfield, pp 175. Thomas, 1961, p 47 (No. 343, Amer Lectures in Living Chemistry, Bonnerstone Division)
24. Mohler ER, Jr, Freis ED: Five-year survival of patients with malignant hypertension treated with antihypertensive agents. Amer Heart J 60:329-335, 1960.
25. Skolow M, Perloff D: Five-year survival of consecutive patients with malignant hypertension treated with antihypertensive agents. Amer J Cardiol 6:858-863, 1960.
26. Kirkendall WM: The management of hypertension patients with renal insufficiency. Hypertension recent advances. The 2nd Hahnemann Symposium on Hypertension Disease. Brest AN, Moyer JH (eds). Philadelphia: Lea and Febiger, 1961.
27. Langford HG, Bonas JR: Treatment of the uremic hypertensive patient. Mod Treatm 3:62-67, 1966.
28. Schroeder HA: Azotemic malignant hypertension. (Letter to the Editor) New Eng J Med 277:291, 1967.
29. Woods, JW, Blythe WB: Management of malignant hypertension complicated by renal insufficiency: Further experience. Trans Climat Asso 79:108-114, 1967.
30. Mroczek WJ, Davidov M, Gavrilovich L, et al: The value of aggressive therapy in the hypertensive patient with azotension. Circulation 40:893-904, 1969.

## URINARY TRACT INFECTION

### Its Diagnosis and Significance

CPT Michael R. Conger, MC\*

The role of urinary tract infection in the evolution of significant renal disease is a subject of fervent current investigation. The significance of asymptomatic bacteriuria is hotly debated. This paper will attempt to clarify why there is a disparity of thought on this subject and bring the presently known facts together so that the reader will be able to appraise critically future references to the topic.

#### Diagnosis of urinary tract infection

There is no problem diagnosing urinary tract infection in the patient with fever, flank pain, dysuria, and pyuria. The problem lies in determining the significance of symptoms with a normal urinary sediment or bacteriuria in the absence of symptoms. TABLE I outlines a few common reasons for the misdiagnosis of urinary tract infections.

A frequently confusing problem is the finding of pyuria in a "routine" urinalysis. Although this finding should alert one to a diagnosis of infection, pyuria can occur in the absence of bacteriuria. TABLE II outlines the nonbacterial causes of pyuria which must also be considered when it is discovered. When urine cultures are sterile in such instances (or have an insignificant bacterial growth), genitourinary tract tuberculosis should be considered and excluded by obtaining at least three morning urines for Ziehl-Neelson staining and cultures.

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TABLE I  
REASONS FOR MISDIAGNOSIS OF URINARY TRACT INFECTION

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→PYURIA (5 WBC/HPF SPUN URINE)
occurs only in 50 percent of women with asymptomatic bacteriuria
occurs in the absence of bacteriuria
→"WBC CASTS"
may come from prostate
→POSTERIOR URETHRAL INFECTION
may occur in patients without bacteriuria
→DYSURIA
may not mean bladder infection even with 1000- 10,000 organisms per milliliter
→BACTERIURIA
exists asymptotically

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TABLE II  
NON-BACTERIAL CAUSES OF PYURIA

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GLOMERULONEPHRITIS
LUPUS NEPHRITIS
RENAL TUBULAR CELLS MISDIAGNOSED AS WHITE BLOOD CELLS
BLADDER TUMORS
URETHRITIS ( <i>Trichomonas</i> )

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Although glomerulonephritis or lupus nephritis cause pyuria, they should be apparent from other clinical manifestations. Renal tubule cells resemble white blood cells but can be differentiated from them by the use of peroxidase stain (Sedi-stain<sup>(R)</sup>). Bladder tumors should be considered as a cause of pyuria when the patient is past forty or has a history of exposure to aniline dyes or heavy cigarette smoking. Urethritis without infection of the urine can often be confirmed by comparing a two-part urine collection. Trichomoniasis as a cause of pyuria can be determined by examination of the sediment and recognition of the organism. It is therefore apparent that symptomatology and urinalysis may aid in diagnosing urinary tract infection, but the urine culture is still required to confirm it.

Urine is normally sterile. It had been theorized that showers of bacteria occurring normally could cause a low titer of bacteria to appear in the urine via glomerular filtration. Stamey and Pfau /1/, however, gave intravenous bacterial injections to dogs without resultant bacteriuria. Thus there is strong evidence that bacteremia does not induce bacteriuria in nonobstructed individuals. Despite the known sterility of urine, it has been shown that only two percent of women with sterile urine, as proven by suprapubic needle aspiration, have a sterile midstream collection. Figure 1. We are therefore obligated to develop some ground rules for deciding the significance of a positive culture. If the female perineum is meticulously scrubbed and a total voided specimen contains more than  $10^5$  organisms per milliliter, there is an 80 percent chance that the patient has a urinary tract infection. Two such positive specimens gives a 91 percent chance that the patient is infected, and three such cultures gives a 95 percent chance. /2/ Realistically, however, waiting for two or three consecutive procedures to approach a respectable range of error represents a serious time delay as well as additional expense. Also, this statistical presentation does not tell one how many people with less than  $10^5$  bacteria have significant infection and many physicians have misinterpreted these figures to mean that no one with less than  $10^5$  organisms per milliliter has a significant infection. Stamey and Pfau /1/ list three alternatives to the total voiding cultures which can avoid these problems: (1) suprapubic needle aspiration of the bladder, (2) midstream urine specimen collected on lithotomy table after nurse cleans the perineum, and (3) catheterization of the bladder.

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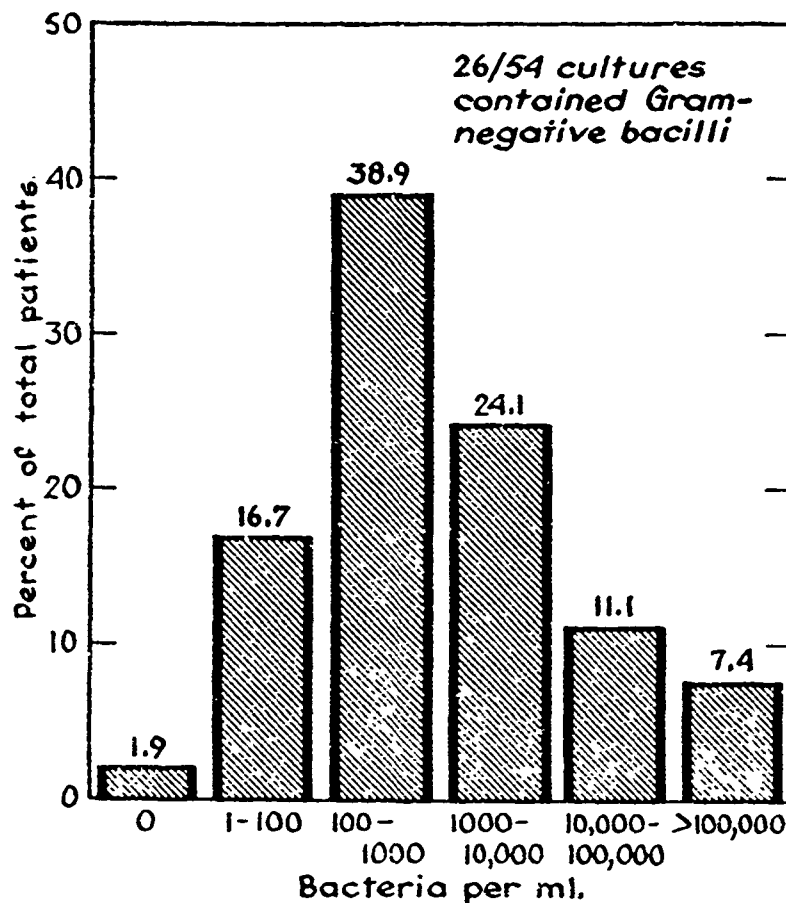


Fig 1. Midstream bacterial counts in 54 females with sterile suprapubic bladder aspirations. [11]  
 (Reproduced by permission of the authors and The Williams and Wilkins Co., publishers.)

Needle aspiration of the bladder is safe, offers a 99 percent confidence level for obtaining sterile urine, and is painless, but may be emotionally distressing to the patient. Stamey and Pfau [1] suggest that collecting a midstream specimen from a patient on a cystoscopy table after a trained nurse has thoroughly cleansed her perineum is nearly as efficient (95 percent confidence level). Figure 2. This is not practical for most physicians, however. Although catheterization is an accurate way of diagnosing urinary tract infections, there is the risk of causing an infection. The risk is reasonably small in outpatients without a urinary tract abnormality, but in any hospitalized patient the incidence of infection is high -- as high as 20 percent on a medical ward according to one report. [3] If a patient

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needs catheterization because of obstruction it should not be avoided, but to use a catheter for diagnosis may lead to a morbidity of its own.

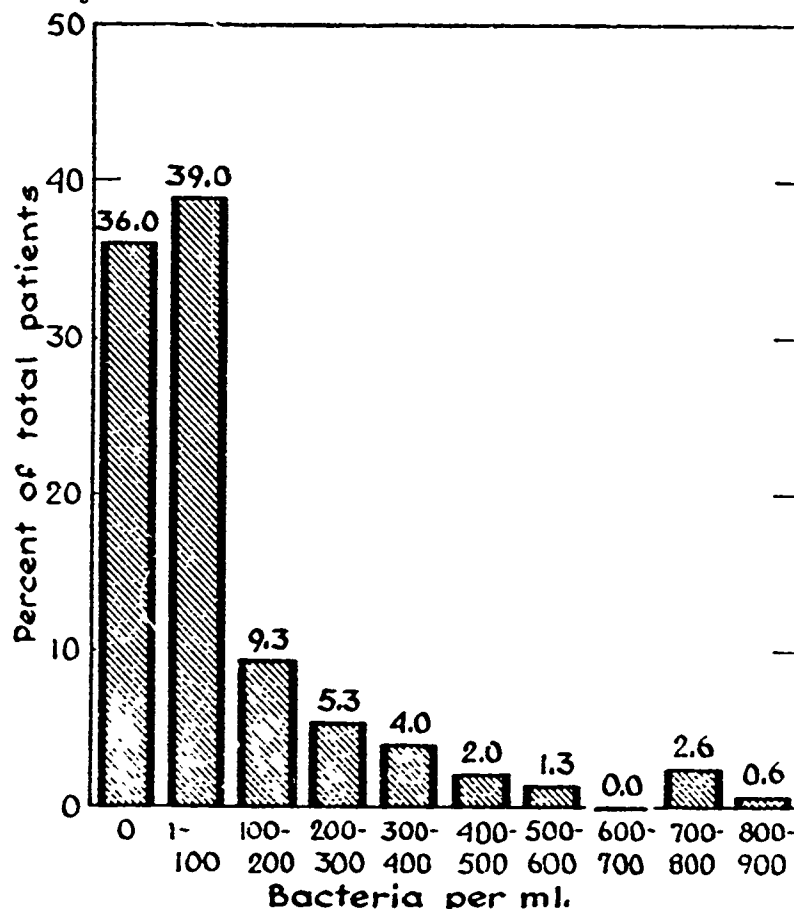


Fig. 2. Midstream cultures voided from cystoscopy table in 151 females with sterile suprapubic bladder aspirations [11]. (Reproduced by permission of the authors and The Williams and Wilkins Co., publishers.)

For normal use, a midstream specimen after the patient cleanses the perineum would seem to be the best method if the patient is reliable. Results should probably be confirmed by a second specimen. If patient displays poor hygiene or is unable to follow instructions, a midstream collection following a perineal scrub by a nurse would be advisable. A suprapubic needle aspiration would be a reasonable alternative and should be considered in cases where the diagnosis is questionable by other means.

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In determining the significance of a colony count, despite the care (or lack of it) with which the specimen is collected, one should be cognizant of the type of organisms cultured because lactobacilli, streptococci (except enterococci), and staphylococci (other than in diabetic patients) are usually contaminants. Such organisms when present in large numbers generally signify a poorly collected specimen and call for another carefully obtained specimen. Some pitfalls must also be avoided which might falsely lower a significant urinary bacterial count, such as antibiotic therapy, hydration, frequency of voiding, fastidious organisms, and contamination of the specimen by soap.

*Significance of Urinary Tract Infections*

The incidence of bacteriuria in various population groups is well-established. It varies from four percent in males seen in the medical outpatient department to almost 100 percent in patients with indwelling catheters for over 96 hours. /9/

The rarity of bacteriuria in young males has been documented by Kunin's work /5/ in which he reported only two positive cultures in 7,731 boys and young men, 1,116 of whom were between the ages of 15 and 29 years.

To enable one to estimate prognosis and judge the effect of therapy, urinary tract infection has been conveniently divided into four categories /6/: (1) uncomplicated acute urinary tract infections, (2) complicated acute urinary tract infections, (3) asymptomatic bacteriuria of unknown duration, and (4) chronic bacteriuria.

Acute urinary tract infection may often be self-limited but should be treated because in a few instances it is followed by chronic bacteriuria. With repeat episodes of infection a thorough evaluation should be undertaken and all young men should have a complete urologic evaluation at the time of their first episode. Complicated urinary tract infections are acute episodes and a structural abnormality is present. The infection will not usually be cured until the anatomic defect is corrected.

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Asymptomatic bacteriuria is usually a problem of females and a careful history will often reveal previously undescribed symptoms of urinary tract infection. A number of these patients will also go on to develop subsequently symptomatic infections. Chronic bacteriuria means persistent bacteriuria with repeated symptomatic intervals interspersed with asymptomatic intervals. Many of these patients have an associated obstructive uropathy. These infections are often resistant to treatment for a number of reasons including resistant bacteria, obstruction, renal calculi (which are a constant reservoir of infection), emergence of antibiotic-resistant mutants, and an environment unfavorable to antibiotic action in the renal parenchyma. The possibility that local and humoral mechanisms in the kidney are not favorable to eradication of the infection may also account for the failure of adequate treatment.

### *The Danger of Chronic Infection*

It is an inherent quality of physicians which makes them want to treat and eradicate any pathologic condition. The presence of asymptomatic or chronic bacteriuria is a prime example of such a situation, but workers in this area are having difficulty deciding whether or not the mere presence of bacteria in urine is dangerous.

There is no indication that chronic bacteriuria does any permanent damage to the urethra or to the bladder, however, a great deal of controversy revolves around whether or not chronic bacteriuria leads to chronic pyelonephritis. The controversy is made almost unresolvable by a complete lack of agreement on a definition of pyelonephritis as reflected in the comment by Petersdorf and Turck /6/:

. . . Nephrologists tend to equate pyelonephritis a disease characterized predominantly by tubular dysfunction that eventuates in uremia; urologists think of pyelonephritis in terms of obstructive uropathy and vesicoureteral reflux as forerunners of infection; pediatricians think of pyelonephritis as a disease associated with congenital abnormalities that lead to repeated infections, failure to thrive, and renal insufficiency; and pathologists are still struggling with the problem of how to define the

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disease morphologically and to establish a relationship between a specific histologic picture and a variety of pathogenic stimuli, including analgesic ingestions, irradiation, potassium depletion, hypertension, and infection.

It is known that a large percentage of pregnant women with untreated bacteriuria will develop acute pyelonephritis. Savage et al /7/ reported that 26 percent of those untreated versus zero percent of the treated women in a double blind study developed acute pyelonephritis before the termination of the pregnancy. Therefore, a strong recommendation for treatment of bacteriuria in pregnancy is made especially to prevent acute pyelonephritis. An association with prematurity, perinatal death, and toxemia has been suggested, but this demands further study. /7,8/

Studies /9-11, have shown that approximately 50 percent of patients with recurrent bacteriuria have culturable bacteria obtainable from the ureter. Renal pelvic bacteriuria has been taken by many to mean that this is consistent with chronic pyelonephritis, but this has never been proven. Stamey and Pfau /1/ prefers to call this "pyelitis".

There is a defect in the concentrating ability of the kidney in chronic pyelonephritis. TABLE III. A similar defect has been demonstrated in cases of renal bacteriuria and, more importantly, this defect existed only on the bacteriuric side in patients who did not have renal bacteriuria bilaterally. This concentrating defect improves following eradication of the bacteriuria. /12/ Some people consider this evidence for chronic pyelonephritis, however, this is merely "guilt by association". According to Stamey and Pfau /1/ no one has proven that bacteria in the renal pelvis lead to chronic destruction of renal tissue. Both chronic pyelonephritis and pelvic bacteriuria could cause a defect in concentrating ability.

Hemagglutination studies demonstrated higher titers of antibodies to bacteria in cases of acute pyelonephritis than they do in cystitis. The persistence of antibody titers is also observed in patients with chronic pyelonephritis from whom bacteria cannot be cultured. /7,13/ Guttman et al /14/ showed that in 57 patients with sterile urine and chronic pyelonephritis, 11 had bacterial

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variants in their urine. These variants which are difficult to culture could explain the existence of titers in patients without culturable bacteria but whether or not this is related to chronic pyelonephritis is yet to be proven.

TABLE III

## CONCENTRATING ABILITY IN MILLIOSMOLES\*

	Right Kidney	Left Kidney
BLADDER BACTERIURIA	936.1	918
	Infected Kidney	Non-Infected Kidney
RENAL BACTERIURIA	675	875
	Initial	After Irradiation
AFTER IRRADIATION OF INFECTION	731	762

\*Adapted from Ronald, et al: *Ann Intern Med* 70:723-733, 1969

Stamey and Pfau /1/ believe that the only way to determine the existence of pyelonephritis is by intravenous urograms that show destruction of the renal cortex. A recent intravenous pyelograph study in two parts, /15,16/ done in Wales showed no evidence of chronic progressive pyelonephritis in 93 women with chronic bacteriuria, 50 percent of whom were over the age of 45 years. Aoki et al /17/ showed by immunofluorescence the presence in the kidney of bacterial antigen in six of seven patients with "a bacterial" pyelonephritis. Again there is no proof that this leads to chronic pyelonephritis. A point against its leading to chronic pyelonephritis was made by Sanford and Barnett /18/ when they showed that the existence of antigen following acute pyelonephritis in rats did not lead to progressive scarring and loss of tissue.

Even though bacteriuria is ten times more common in females than in males, this sexual predominance is not seen in chronic pyelonephritis. This would point away from bacteriuria as a

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cause of chronic pyelonephritis. /1/

Freedman /19/ in an autopsy review, found 64 cases of chronic, nonobstructive pyelonephritis. Only 15 of these cases died with uremia, and of these 15 only one had a history of urinary tract infections during life, and only two had positive cultures prior to the onset of uremia.\* Fourteen of the 15, however, had a history of other disease predisposing to renal disease.

*COMMENT*

The majority of the current evidence points toward the fact that bacteriuria has little to do with the development of chronic renal disease, however, future work should always be considered with an open mind.

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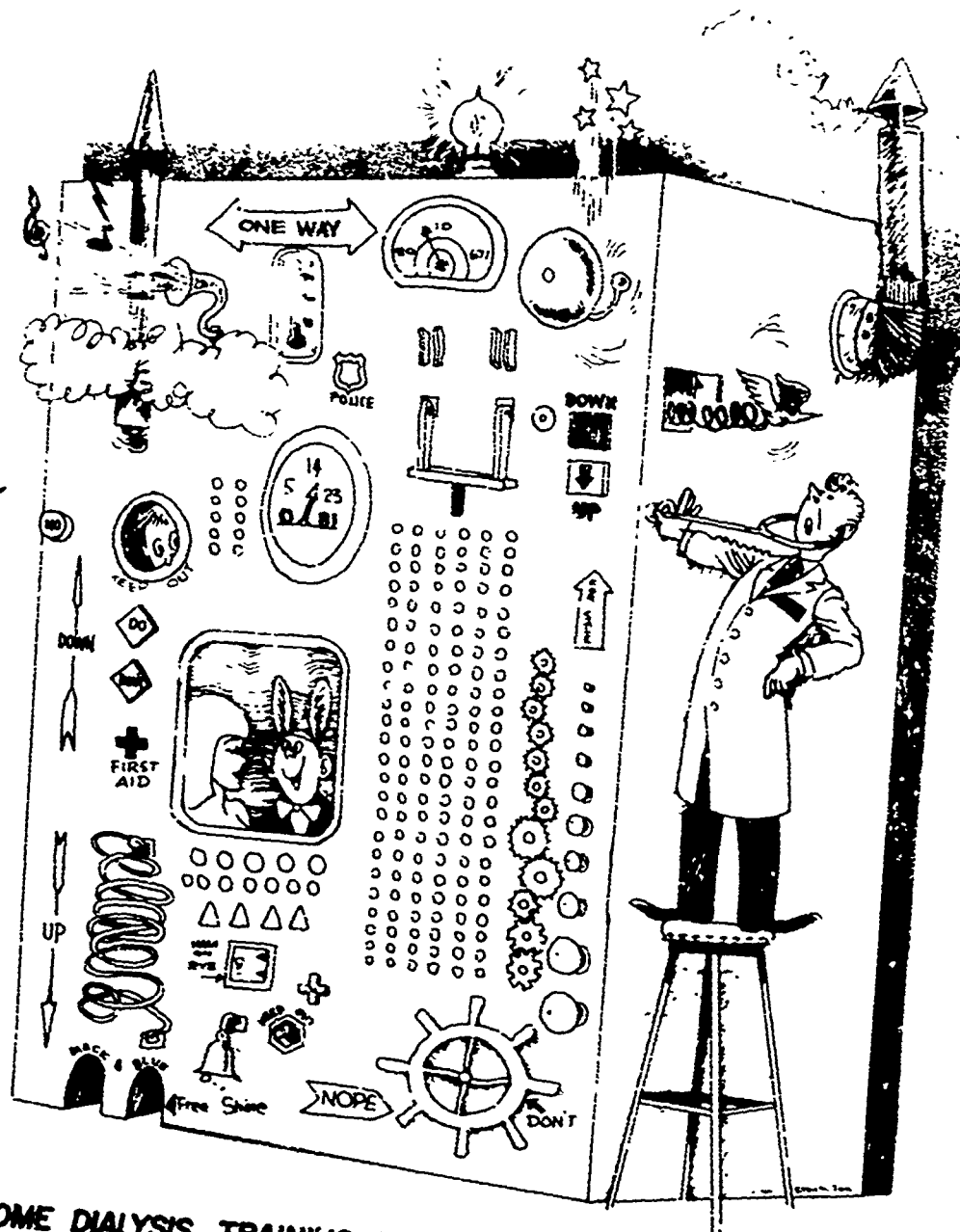
\*This might suggest that "abacterial" pyelonephritis, i.e. an immunologic phenomenon, is an important factor (11)

*References*

1. Stamey TA, Pfau A: Urinary infections: A selective review and some observations. Calif Med 113:16-35, 1970
2. Kass EH: Asymptomatic infections of the urinary tract. Trans Amer Ass Physicians 69:56-63, 1956
3. Turck M, Gotte B, Petersdorf RG: The urethral catheter and urinary tract infection. J Urol 88:834-837, 1962
4. Kass EH: The role of asymptomatic bacteriuria in the pathogenesis of pyelonephritis. Biology of Pyelonephritis, Quinn EL, Kass EH (eds). Boston: Little, Brown and Company, 1960, pp 399-412
5. Kunin CM, Zacha E, Paguin AJ: Urinary tract infection in school children. I. Prevalence of bacteriuria and associated urologic findings. New Eng J Med 266:1287-1296, 1962
6. Petersdorf RG, Turck M: Some current concepts of urinary tract infections. Disease-a-Month December 1970

*Urinary Tract Infection - Conter*

7. Savage EW, Haji SN, Kass EH, et al: Demographic and prognostic characteristics of bacteriuria in pregnancy. Medicine 46:385-407, 1967
8. Wilson MG, Hewitt WL, Monzon OT: Effect of bacteriuria on the fetus. New Eng J Med 274:1115-1118, 1966
9. Turck M, Anderson KN, Petersdorf RG: Relapse and reinfection in chronic bacteriuria. New Eng J Med 275:70-77, 1966
10. Turck M, Ronald AR, Petersdorf RG: Relapse and reinfection in chronic bacteriuria. II. The correlation between site of infection and pattern of recurrence in chronic bacteriuria. New Eng J Med 278:422-427, 1968
11. Stamey TA, Govan DE, Palmer JM: The localization and treatment of urinary tract infections: The role of bactericidal urine levels as opposed to serum levels. Medicine 44:1-36, 1965
12. Ronald AR, Cutler RE, Turck M: Effect of bacteriuria on renal concentrating mechanisms. Ann Intern Med 70:723-733, 1969
13. Carter MJ, Ehrenkranz J, Burns J, et al: Serologic response to heterologous escherichia sero groups in women with pyelonephritis. New Eng J Med 279:1407-1412, 1968
14. Guttman LT, Turck M, Petersdorf RG, et al: Significance of bacterial variants in urine of patients with chronic pyelonephritis. J Clin Invest 44:1945-1952, 1965
15. Sussman M, Asscher AW, Waters WE, et al: Asymptomatic significant bacteriuria in the nonpregnant woman. I. Description of population. Brit Med J 1:799-803, 1967
16. Asscher HW, Sussman M, Waters WE, et al: Asymptomatic significant bacteriuria in the nonpregnant woman. II. Response to treatment and follow up. Brit Med J 1:804-806, 1967
17. Aoki S, Imamura S, Aoki M, et al: "Abacterial" and bacterial pyelonephritis. New Eng J Med 281:1375-1382, 1967
18. Sanford JP, Barnett JA: Immunologic studies in urinary tract infections. Prognostic and diagnostic. JAMA 192:587-592, 1965
19. Freedman LR: Chronic pyelonephritis at autopsy. Ann Intern Med 66:697-710, 1967



HOME DIALYSIS TRAINING IS EASY AS PIE !

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## MANAGEMENT OF ACUTE INTOXICATION WITH BARBITURATES, HEROIN AND LSD

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### BARBITURATE INTOXICATION

Barbiturates remain the drug most often reported as the cause of poisoning in adults in the United States. A fairly recent estimate suggests there are more than 15,000 hospitalizations and 1,000 deaths annually from such intoxications. Because of the current drug culture evolving in the country and particularly in our own community, this is probably a gross underestimation. In addition to the former classical case of acute massive ingestion for suicidal reasons, a new class of overdose problem is being seen in greater numbers. These are the chronic barbiturate abusers who regularly take 15 to 20 "reds" or "yellows" per day and who are seen as acute overdose problems when they abruptly increase their intake to 30 or 40 capsules in a given day, either through despondency or actual error in judgment in calculating the dose required to produce the desired effect. Presumably because of tolerance or enzyme induction, these intoxications tend to take a milder course, but their treatment is complicated by the possibility of the potentially lethal barbiturate withdrawal syndrome if the background of chronic abuse is unrecognized. The signs and symptoms are given in TABLE I.

#### Treatment

Necessary treatment for mild intoxications as in recent ingestion or low dosage may be only induction of emesis (if the patient is alert) or lavage and observation if the patient is only mildly depressed. Emesis may be induced by injections of apomorphine, 0.07 mg/kg of body weight. Emesis is more effective if the stomach contains liquid. Nalorphine should be immediately accessible in the event that apomorphine produces

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TABLE I  
SYMPTOMS AND SIGNS OF DRUG ABUSE\*\*

AGENT OF ABUSE	ACUTE INTOXICATION	WITHDRAWAL SYNDROME
Barbiturates, Meperidine, and other central nervous system depressants	Pupils normal; blood pressure and respiration depressed; nystagmus on lateral gaze, tendon reflexes depressed; ataxia, slurred speech; coma; shock, Confusion.	Tremulousness; insomnia; high fever, clonic blink reflex; convulsive seizures; cardiovascular collapse. Agitation; delirium; psychosis.
Narcotics	Pupils pinpoint, fixed; blood pressure and respiration depressed; coma; shock; pulmonary edema. Sensorium depressed, although some patients may be alert and appear normal.	Pupils dilated, reactive to light pulse rate, blood pressure, temperature, and respiratory rate elevated; muscular aches and twitches; nausea, vomiting; diarrhea; dehydration, weakness, chills, rhinorrhea lacrimation; gooseflesh, yawning, restlessness, followed by sleep.
Hallucinogens* LSD Type LSD Psilocybin Mescaline STP DMT	Pupils dilated, reactive to light, blood pressure elevated; tendon reflexes hyperactive; sweating; gooseflesh, Anxiety; sensorium often clear; distortion of body image and of sensory perception; kaleidoscopic visual hallucinations; delusions.	No specific syndrome.
Anticholinergics Atropine Scopolamine Belladonna Antihistamines	Pupils dilated; fixed; flushed dry skin and mucosa; urinary retention. Sensorium cloudy, disorientation; amnesia; nonsensical answers; visual hallucinations without perceptual distortion; body image altered.	No specific syndrome.

\*These depend largely on dosage and duration of abuse.

†From *The Medical Letter*, August 1976.

\*Other hallucinogens used are: peyote, mescaline, psilocyline, 2,5-dimethoxy-4 methyl amphetamine (STP), dimethyl tryptamine (DMT), methylenedioxyamphetamine (MDA), N,N dimethyl tryptamine (DMT), methoxymethylene and dioxymethylene (TMA), methoxymethylene (TMA), methoxymethylene (TMA), thioethanidin (THC), phenylethylamine (PEA) and various solvents.

respiratory depression. If lavage is done, it will be most effective if 2-3 liters of saline containing a slurry of at least 1 gm/kg activated charcoal (powder, not tablets) is used. The charcoal quantitatively absorbs the drug and prevents its absorption by the gastrointestinal tract. Following lavage 30-90 ml of castor oil is instilled into the stomach. The lipid soluble drug is selectively dissolved into the non absorbable oil which removes the remainder of the drug from the bowel. In the presence of even minimal depression, oil instillation should not be done unless a cuffed nasotracheal tube is in place and inflated.

Any patient who will tolerate an endotracheal tube requires it. The cuff should be deflated 15 minutes every 2 hours, and tracheobronchial suctioning with aseptic technique should be faithfully performed as frequently as necessary. With any degree of hypoventilation and certainly if the  $pO_2$  is 70 mm Hg or less, mechanical assistance should be provided. A head down position and frequent turning help prevent atelectasis. With prolonged coma, aspiration or bacterial pneumonitis is common and tests for this should be frequent. Gram-negative infections are common. A simple oxygen saturation test has recently been described which will detect aspiration pneumonia before clinical or radiological findings are present. Maintenance of adequate airway and ventilation is the single most important aspect of sedative overdose management.

#### Hypotension

Barbiturates and most other sedatives produce vasodilation and relative hypovolemia. Surprisingly large amounts of plasma expanders may be required to produce a normal central venous pressure (CVP), tissue perfusion and glomerular filtration. Vasopressors, preferably with inotropic action should be used rarely and only when it is certain that effective circulating plasma volume is normal. If renal perfusion is adequate blood pressures somewhat lower than those usually considered normal are acceptable in the comatose, totally relaxed patient.

*Management of Drug Abuse - Shumberger***Hypothermia**

Rewarming to prevent ventricular fibrillation is indicated if body temperature falls to 32 C.

**Forced Diuresis**

With the exception of phenobarbital, the barbiturates have pK values higher than physiological pH and are not excreted in the active form in significant amounts in the urine. The excretion of phenobarbital (pK 7.2) can be significantly increased by forced alkaline diuresis provided the urinary pH is maintained above this level. The excretion of short-acting barbiturates can be increased about 20 percent by forced osmotic diuresis. The increased clearance is related to the increased urine flow. Since flow rates above 100 ml/hr are required, careful attention to replacement of electrolytes is necessary. An additional 40 ml/hr should be given for insensible loss (less if on respirator, more if fever is present).

**Dialysis**

Peritoneal dialysis is relatively inefficient for removal of barbiturates, but is occasionally necessary in children. Hemodialysis should be considered when the following factors are present: (1) the patient is elderly, (2) there are complicating diseases, (3) failure to improve with conservative management, and (4) blood levels are 3.0 mg/100 cc short-acting or 7 mg/100 cc long-acting. Hemodialysis is somewhat less effective for short-acting barbiturates and dialysis with lipid dialysate may be considered. If dialysis is elected, careful attention to all of the general supportive measures must be maintained throughout the procedure.

**Psychiatric Assistance**

The most important time for the psychiatric evaluation and therapy is immediately after awakening.

## CHRONIC BARBITURATE ABUSE

## THE BARBITURATE ABSTINENCE SYNDROME

Chronic barbiturate abuse has become extremely widespread and a special note regarding the barbiturate abstinence syndrome is included because of its medical importance. Barbituric acid was synthesized in 1863 and barbital was introduced into medical practice in 1903. Chronic intoxication and convulsions upon withdrawal were described in Germany as early as 1905. Subsequent reports of barbiturate dependency went unheeded until the studies of Isbell and co-workers in 1950 who did controlled experiments in man which demonstrated conclusively that the abuse of barbiturates can induce physical dependency. The intoxication syndrome resembles alcoholic intoxication and is characterized by lethargy or somnolence, wide-based staggering gait, nystagmus on lateral gaze, slurred speech, impaired judgment, and emotional lability. The abstinence syndrome is far more serious than the abstinence syndrome of opiate addiction. Not only are convulsions and temporary psychosis liable to develop, but death may occur. Minor abstinence manifestations include apprehension, muscular weakness, tremulousness, postural fainting due to postural hypotension, gastrointestinal disturbances and muscular twitching. Major manifestations include one or all of the following: generalized tonic-clonic convulsions, psychotic delirium, fever, and death. Up to 100 mg of pentobarbital per day can be taken safely without developing major abstinence manifestation. Above that level, the percentage of incidence of major withdrawal abstinence syndrome varies directly with increasing daily dose. Convulsions may develop as early as 16 hours, but usually occur on the second or third day of withdrawal. The development of temperature above 101 F during withdrawal is an indication for vigorous treatment. Diphenylhydantoin has never been demonstrated to offer protection from barbiturate withdrawal seizures. Abrupt withdrawal from meprobamate, glutethimide, methyprylon, ethinamate, ethchlorvinyl, chlordiazpoxide, and diazepam has been reported to result in grand mal seizures, psychotic behavior, or both.

Recently Smith and Wesson<sup>2</sup> have proposed a safe method for barbiturate withdrawal. Basically, the daily dose of barbiturate, which is practically always secobarbital or pentobarbital, is estimated by history from the abuser. This is usually from 500 to 3000 milligrams. Each 100 mg of short acting barbiturate is equated to 32 mg of phenobarbital and this is given as total daily dose divided into four doses which are somewhat higher in the evening than in the mornings. After two days of stabilization and close observation, the total daily dose is decreased by 30 mg per day. If symptoms develop during withdrawal an injection of 200 mg of phenobarbital is given immediately and the decrease in dosage is discontinued until withdrawal symptoms have subsided.

<sup>1</sup>Isaelli H, Alschul S, Kornetsky C, et al: Chronic barbiturate intoxication. An experimental study. *Arch Neurol Psychiat* 64:1-28, 1950

<sup>2</sup>Smith DE, Wesson DR: Phenobarbital technique for treatment of barbiturate dependency. *Arch Gen Psychiat* 24:56-60, 1971

#### HEROIN OVERDOSE

Severe overdose may be almost instantly fatal and is not amenable to treatment. Overdose produces pinpoint pupils, depressed blood pressure and respiration, coma, shock, and pulmonary edema. Diagnosis usually easy from "tracks" or evidence of "skin popping". The signs and symptoms are listed in TABLE I.

#### Treatment

Immediate injection of nalorphine 2-10 mg (if no veins are usable, inject into sublingual venous plexus). Repeat as often as necessary to prevent recurrence of apnea or hypotension. Response is judged by dilation of pupils. Hypotension may require plasma expanders and pressors. These patients should be observed for at least eight hours because pulmonary

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edema may appear later and be fatal. Treatment consists of diuretics, oxygen, tourniquets, and occasionally digitalis. The precise etiology of the pulmonary edema is unknown. Theories include: (1) overdose of the common adulterant quinine, (2) particulate thrombo-embolism, (3) hypoxia, and (4) anaphylactic reaction with lung as target organ. Addicts are also susceptible to staphylococcal pneumonia and endocarditis. It should be remembered that the nalorphine used in treatment may produce an abrupt withdrawal syndrome which may require treatment.

LYSERGIC ACID DIETHYLAMIDE (LSD)

Making a diagnosis on basis of history of LSD ingestion is risky since much of what is sold as LSD is actually phen- cyclidine (sernylan), strychnine, amphetamines and atropine. TABLE I includes typical signs and symptoms. LSD and other hallucinogens induce a hypersuggestible state that can be exploited by reassurance. Hyperactivity can be controlled by "talking the patient down." Urge the patient to keep his eyes open since this usually decreases the panic and hallucinations. Although the phenothiazines are useful when sedation is necessary, their use can be hazardous when an anticholinergic drug has been mixed with the LSD as severe hypotension can be produced. TABLE I. Excessive dryness of the mouth and absence of sweating are clues to possible adulteration with anticholinergics. If an "anticholinergic crisis" is produced by treatment with phenothiazines, 2-4 mg physostigmine given intramuscularly and repeated as often as necessary may reverse the crisis. It may be safer to use parenteral Librium® or Valium® and to rely heavily on reassurance.



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